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Humoral immune response following SARS-CoV-2 mRNA vaccination concomitant to anti-CD20 therapy in multiple sclerosis☆

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ABSTRACT

Background: The immunogenicity of COVID-19 vaccine among patients receiving anti-CD20 monoclonal antibody (Ab) treatment has not been fully investigated. Detectable levels of SARS-CoV-2 immunoglobulin G (IgG) are believed to have a predictive value for immune protection against COVID-19 and is currently a surrogate indicator for vaccine efficacy.
Objective: To determine IgG Abs in anti-CD20 treated patients with multiple sclerosis (MS).
Method: IgG Abs against SARS-CoV-2 spike receptor–binding domain were measured with the SARS-CoV-2 IgG II Quant assay (Abbott Laboratories) before and after vaccination ($n = 60$).
Results: 36.7% of patients mounted a positive SARS-CoV-2 spike Ab response after the second dose of vaccine. Five patients (8.3%) developed Abs >264 BAU/mL, another 12 patients (20%) developed intermediate Abs between 54 BAU/mL and 264 BAU/mL and five patients (8.3%) had low levels <54 BAU/mL. Of all seropositive patients, 63.6% converted from seronegative to seropositive after the 2nd vaccine.
Conclusion: Our study demonstrates decreased humoral response after BNT162b2 mRNA SARS-CoV-2 vaccine in MS patients receiving B-cell depleting therapy. Clinicians should advise patients treated with anti-CD20 to avoid exposure to SARS-CoV-2. Future studies should investigate the implications of a third booster vaccine in patients with low or absent Abs after vaccination.

1. Introduction

Chimeric rituximab, humanized ocrelizumab and human ofatumumab are categorized as anti-CD20 therapies causing lysis of B-cells. These therapies are commonly used in a wide spectrum of inflammatory/autoimmune diseases and blood cancers, including rheumatoid arthritis, multiple sclerosis (MS) and neuromyelitis optica in neurology and lymphoma and leukaemia in hematology. Unfortunately, during the COVID19 pandemic, more severe complications of SARS-CoV-2 infection have been associated with anti-CD20 therapy in patients with MS (Sormani et al., 2021; Salter et al., 2021), prompting several treatment dilemmas for patients and their clinicians. These include risk of MS flares when extending treatment intervals, safety concerns regarding COVID-19 and the necessity of protection with vaccination, and vaccine

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efficacy in B-cell depleted patients (Rolfes et al., 2021; EMA 2018).

Worldwide, use of mRNA-based SARS-CoV-2 vaccines for patients treated with anti-CD20 therapy has been recommended. Since the efficacy of vaccines depends both on a humoral and cellular response, levels of SARS-CoV-2 IgG antibodies (Abs) are believed to have a predictive value of immune protection against COVID-19, and are currently used as an indicator of vaccine efficacy (Sormani et al., 2021; Vishnevetsky et al., 2021; Khoury et al., 2021; Gaitzsch et al., 2021; Loarce-Martos et al., 2020; Bachiller-Corral et al., 2021; Addetia et al., 2020). Unfortunately, treatment with anti-CD20 therapies is generally associated with an attenuated humoral response to vaccines. The recent VELOCE study demonstrated decreased humoral response to vaccination against pneumococcal, keyhole limpet hemocyanin, tetanus-toxoid containing vaccine, and influenza in anti-CD20 treated MS patients (Bar-Or et al., 2020). Other studies have also suggested decreased humoral response to vaccines in patient populations treated with anti-CD20 therapy (Achiron et al., 2021). Furthermore, levels of B-cells and dosage intervals of anti-CD20 therapy are believed to affect the response to vaccination (Day et al., 2020; Killestein et al., 2020; Nguyen et al., 2017; Ammitzbøll et al., 2021).

The study hypothesis is that levels of SARS-CoV-2 spike RBD antibodies generated in response to mRNA SARS-CoV-2 vaccines are reduced in MS patients treated with anti-CD20 therapy and that serial vaccination increases the proportion of seropositive. To test this hypothesis, we examined levels of SARS-CoV-2 Abs before and after SARS-CoV-2 vaccination in a cohort of patients on anti-CD20 therapy.

2. Methods

2.1. Study population and design

Adult patients (age $\geq$ 18 years) with MS (2010 McDonald Criteria) and currently treated with anti-CD20 therapy (ocrelizumab) were enrolled in the study before receiving their first mRNA SARS-CoV-2 vaccination. All patients received their care in three Danish MS clinics, South West Jutland Hospital, Hillerød Hospital or Viborg Hospital, or at the University of California, San Francisco, Center for MS and Neuroinflammation. The patients did not receive any other immunosuppressive therapy during this study and were negative to IgG Abs against SARS-CoV-2 prior to inclusion. One patient had a history of COVID-19 and positive polymerase chain reaction nasopharyngeal swab. All patients followed standard clinical practice by their treating neurologist. (Baden et al., 2021; Polack et al., 2020)

2.2. Sample collection

Blood samples were collected at three timepoints: at baseline 0–7 days before first vaccination (V1), 0–7 days before second vaccination (V2), and two to four weeks after second vaccination (V3). Danish patients provided all 3 timepoints; North American patients only V1 and V3.

2.3. Antibody assay and flow cytometry

IgG antibodies against SARS-CoV-2 spike receptor–binding domain (RBD) were determined in plasma samples, using the SARS-CoV-2 IgG II Quant assay (Abbott Laboratories), which is a quantitative chemiluminescent microparticle immunoassay (Abbott, 2021). The assay was performed using the Abbott Alinity I platform in accordance with the manufacturer's instructions. The resulting chemiluminescence in relative light units in comparison with the IgG calibrator/standard, indicates the strength of the response, which reflects the quantity of IgG present. This assay has shown excellent correlation with the first WHO International Standard for anti-SARS-CoV-2 immunoglobulin (NIBSC code 20/136), enabling the issuing of immunogenicity results in standardized units; binding antibody units (BAU)/mL for a binding assay format as the SARS-CoV-2 IgG II Quant assay. The mathematical relationship of the Abbott AU/mL unit to the WHO BAU/mL unit follow the equation BAU/mL = 0.142xAU/mL, corresponding to a cut-off at 7.1 BAU/mL. This assay has documented ability to detect spike RBD IgG vaccine response in longitudinal samples from individuals both with and without prior SARS-CoV-2 infection (Abbott, 2021; Kristiansen et al., 2021). AB-Levels above 254 BAU/ml was defined as sufficient levels. Values between <254 BAU/ml and >54 BAU/ml were considered intermediate and below <54 BAU/ml as low.

Enumeration of B-lymphocytes was performed using fresh EDTA blood stained from the Denmark cohort with the BD Multitest™ 6-color TBNK reagent in BD TruCount tubes. Samples were analyzed on a BD FACSCanto™ II flow cytometer with BD FACSDiva software. Flow cytometry was performed at Danish sites at baseline.

2.4. Data collection

Samples were collected following international guidelines for biobanking (Teunissen et al., 2009). Venous blood was drawn from a cubital vein into evacuated K2-EDTA or heparinzed tubes. Hereafter, blood was centrifuged within 30–60 min after collection at 2000 G for 10 min at 20 °C. Plasma was aliquoted in 500 µL Sarstedt polypropylene tubes and stored at −80 °C until batch analysis (Teunissen et al., 2009).

2.5. Standard protocol approvals, registrations, patient consents and monitoring

All patients gave written and oral consent. The Denmark study was monitored according to the national laws following good clinical practice and approved by the Danish National Committee on Health Research Ethics (Protocol no. S-20200068C) and Danish Data Protection Agency (journal no. 20/19,878). The UCSF study was conducted with institutional review board approval (University of California, San Francisco, Committee on Human Research, protocol # 21–33,240).

2.6. Data availability

Anonymized data will be shared on request from any qualified investigator under approval from the Danish Data Protection Agency.

2.7. Statistical analysis

All data were analysed for normal distribution and continuous data were presented as the median with minimum and maximum values. Kruskal–Wallis test was used for comparison between groups, and a Wilcoxon matched pairs signed ranks test was used for pairwise comparisons.

3. Results

Between the 23rd of February to 24th of June 2021 a total of 60 participants were enrolled from three clinics in Denmark (n = 37) and one in the USA (n = 23). All participants but one received BNT162b2 (remaining patient received mRNA-1273). Participant baseline demographic and clinical characteristics are shown in the table 1. Median age was 47 years (range 24 to 62 years).

3.1. Antibody levels

All participants demonstrated negative SARS-CoV-2 antibodies prior to vaccination with levels <7.1 BAU/ml (Fig. 1). In the Danish cohort, for whom Abs were measured at V2 (n = 37), 5 (13.5%) converted to positive Ab (median BAU/mL: 19.8, range: 9.2 to 254 BAU/mL) at V2. The Ab levels were not statistically different at V2 compared to V1 (p = 0.0625). At V3, where all patients (n = 60) were assessed, we found detectable Abs in 22 (36.7%) patients (median: 74.2 BAU/mL range: 8.5

Table 1
Baseline clinical and demographic characteristics of participants with MS.

	Denmark		USA		Total	
N	37		23		60	
Female, n (%)	29	78.4	14	60.1	43	71.2
Median age, years (min-max)	47	(24–62)	47	(26–61)	47	(24–62)
Time interval between ocrelizumab treatment and vaccine #1, median weeks (min-max)	13.70	(1.9–27.6)	17.45	(3.6–43.0)	15.10	(1.9–43.0)

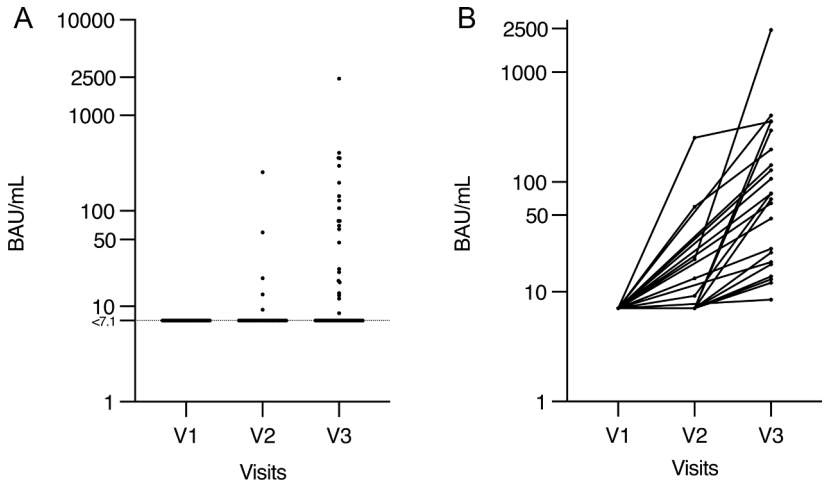

Fig. 1. Depicts levels of antibodies given in BAU/mL.
Graph A: Levels before vaccination at visit 1 (V1), before 2nd vaccine at visit 2 (V2) and two-four weeks after 2nd vaccine at visit 3 (V3).
Graph B outlines the development of each patient with a positive response to the vaccine after and how they convert through each visit.

to 2427 BAU/mL), and levels were statistically higher compared to baseline ($p<0.0001$). In the Danish cohort, 8 of 37 (21.6%) patients were seronegative at V2 (prior to 2nd vaccine) and developed positive Abs at V3.

3.2. Clinical and demographic predictors of Ab detectability

We compared levels of B-cells, age of patients and time since last infusion between patients with and without detectable Abs. (Fig. 2). The median age was 47 years (IQR: 11.5) for the Ab non-detectable group and 44 years (IQR: 17.75) for the Ab detectable group (Fig. 2, A); this difference was not significant. A total of three patients had measurable B-cell values at baseline, one in the Ab non-detectable group and two patients in the Ab-detectable group (Fig. 2, B).

Finally, there was also no significant difference in Ab detectability according to time interval between ocrelizumab infusion and the first vaccination: this interval ranged from 1.9 to 36.7 weeks in the Ab-non-detectable group and from 4.6 to 43.0 weeks in the Ab-detectable group (Fig. 2, C).

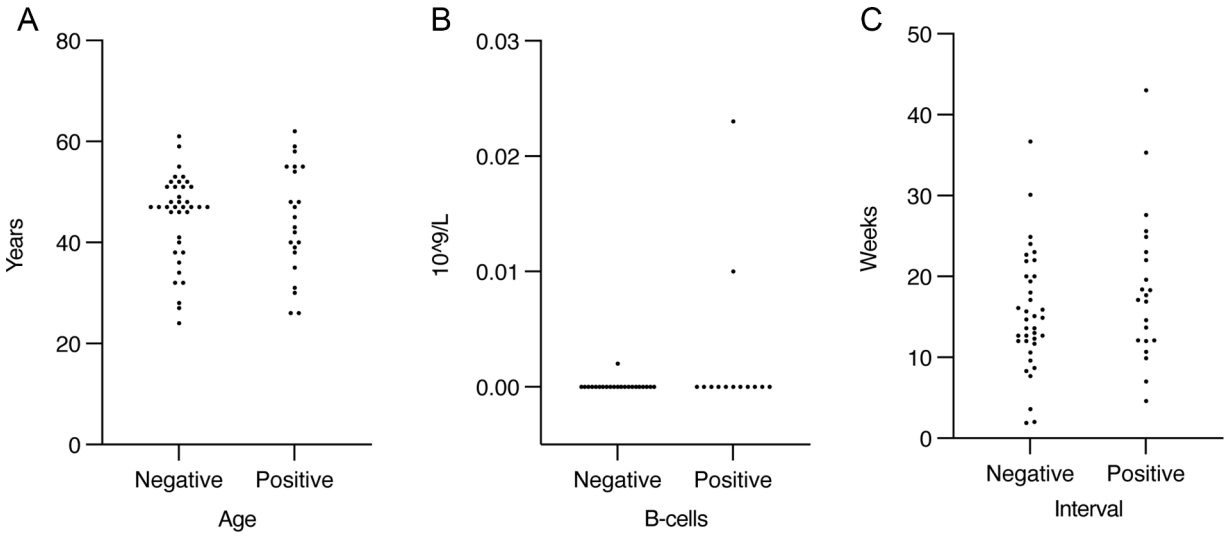

Fig. 2. Graph A: illustrates the distribution of age in patients with a negative and positive response to vaccination.
Graph B: illustrates B-cell count for patients with a negative and positive response to vaccination.
Graph C: illustrates the interval from last infusion with ocrelizumab to visit 1 in patients with a negative and positive response to vaccination.

4. Discussion

In this cohort of 60 patients treated with ocrelizumab prior to SARS-CoV-2 vaccination, we found that 36.7% of patients developed specific Abs. This is a reduced humoral response compared to results from the pivotal trial and from health care workers (Walsh et al., 2020; Maneikis et al., 2021), where almost all vaccinated individuals developed Abs in levels of hundreds to thousands BAU/ml. Immunocompetent vaccinated people develop Abs already one to three weeks after the first vaccine (Polack et al., 2020; Sahin et al., 2021). It is believed that the humoral response, expressed in this study by levels of IgG Abs, reflects an immunological response to vaccination and thereby clinical protection from COVID-19. However, Ab cut-offs portending clinical efficacy has to be established. Our results are comparable to recent publications reporting lower Ab levels in patients with hematological malignancies, rheumatoid arthritis, and MS who are treated with anti-CD20 therapies. In general, patients with blood cancer may *a priori* have a reduced response to vaccination, while patients with untreated MS respond to vaccination similar to healthy controls, indicating that the reduced Ab response is related to the treatment with ocrelizumab (Khoury et al., 2021; Bar-Or et al., 2020; Achiron et al., 2021; Ammitzbøll et al., 2021; Ebinger et al., 2021; Thakkar et al., 2021).

Clinical Ab cut-offs are being established, with recent reports of levels above 264 BAU/mL and 54 BAU/mL providing 80% and 50% protection against COVID-19 infection (Khoury et al., 2021; Feng et al., 2021). In our cohort, there was variable response to vaccination. Five patients (8.3%) developed Abs >264 BAU/mL, another 12 patients (20%) developed intermediate Abs between 54 BAU/mL and 264 BAU/mL and five patients (8.3%) had low levels <54 BAU/mL (Fig. 1, B). Altogether, only a minority of patients treated with anti-CD20 developed sufficient Ab levels, which is similar to what has been reported on other immunosuppressive therapies e.g., solid-organ transplant recipients. Patients with low to intermediate levels of Abs may have decreased protection against COVID-19, which is important knowledge since these patients also tend to have more severe disease course. (Sormani et al., 2021; Khoury et al., 2021; Feng et al., 2021; BJ Boyarsky et al., 2021; BJ Boyarsky et al., 2021).

Our study also suggests a possible effect of serial vaccinations. Prior to 2nd vaccination, only 13.5% developed positive Abs, and a further 21.6% converted from negative to positive after the 2nd vaccination. Of all seropositive patients at V3, 63.6% were negative at V2 and converted after the 2nd vaccine. Those already positive prior to the 2nd vaccine demonstrated higher levels at V3. It has recently been suggested to give a 3rd vaccination to solid-organ transplant recipients that also have suppressed Abs level after both first and second vaccination. These patients were not treated with B-cell depleting therapy and a higher proportion had positive Abs prior to 3rd vaccination (Werbel et al., 2021). Given these findings, our findings of an effect of the second dose, suggest that a 3rd vaccine might potentially convert additional B-cell depleted patients to seropositive status, and increase Ab levels in already Ab-positive patients, to achieve higher protection from COVID-19. Further studies are needed to evaluate this hypothesis and clinical efficacy from an additional vaccination (Werbel et al., 2021; Kamar et al., 2021; Benotmane et al., 2021).

All patients in this study apart from one were without a history of COVID-19. This patient had symptoms of COVID-19 and a positive polymerase chain reaction test for SARS-CoV-2 RNA. This participant demonstrated negative Abs at baseline. One study demonstrated negative Abs one month after COVID-19 in eight patients with MS that were treated with ocrelizumab (Friedli et al., 2021). Another study showed high levels of Abs after vaccination in non-MS patients with a history of COVID-19 (Ebinger et al., 2021). The patient in our study developed low positive Ab levels (8.5 BAU/ml). It is therefore possible that anti-CD20-therapies may lead to an absent antibody response to SARS-CoV2-vaccines and COVID-19.

The timing of vaccination with respect to infusion cycle has been debated during the COVID-19 pandemic. The ocrelizumab product insert suggests that vaccination should be ended six weeks prior to infusion (EMA 2018). However, we found no difference in Ab detectability according to timing since last infusion. Patients received no treatment with anti-CD20 in between the two vaccine injections and at sampling, our patients had up to 43 weeks since last infusion. Two studies found higher probability of seroconversion when vaccination was administrated more than three months after the last ocrelizumab infusion (Achiron et al., 2021; Louapre et al., 2021). Our study could not reproduce this finding.

Extending dosage interval could also potentially increase the risk of MS disease activity. Clinicians must balance between risk of disease activity and the need for protection against COVID-19 when giving advice to patients (Khoury et al., 2021; Feng et al., 2021; Baker et al., 2020).

One limitation of our study is that the cellular response was not examined, limiting our conclusions only to the humoral response. Second, sample collection protocols were selected to support rapid generation of scientific data, but were not always complete. Potentially informative samples that were missing include: no blood samples between 1st and 2nd vaccine, flow cytometry only performed at baseline in approximately two-thirds of participants, and B-cell levels only available at baseline and not before the 2nd vaccination. We could not demonstrate correlation of Abs and levels of B-cells. However this could be related to the low number of patients ($n = 3$) with measureable levels of B-cells.

Altogether, our study demonstrates a decreased humoral response after BNT162b2 mRNA SARS-CoV-2 vaccine in patients receiving B-cell depleting therapy. Clinicians should advise patients treated with anti-CD20 to avoid exposure to SARS-CoV-2, since the efficacy from the vaccine is likely to be reduced. The increased humoral response between the first and the second dose, indicate that a third dose could be considered in this vulnerable group of patients. Further studies are needed to evaluate the relationships between Ab levels, infection susceptibility and clinical outcomes, together with the implications of additional vaccine boosters in patients receiving anti-CD20 therapy.

5. Disclosures

F Novak, A C Nilsson, KE Byg, I S Johansen, C Nielsen, D K Holm, A B Jacobsen, K Mittl, W Rowles, K Mcpolin, C Spencer, S Sagan, C Gerungan, and J Sabatino have nothing to disclose

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CRediT authorship contribution statement

Frederik Novak: Conceptualization, Project administration, Formal analysis. **Anna Christine Nilsson:** Formal analysis. **Christian Nielsen:** Formal analysis. **Dorte K. Holm:** . **Kamilla Østergaard:** . **Anna Bystrup:** . **Keld-Erik Byg:** . **Isik S. Johansen:** Conceptualization. **Kristen Mittl:** Formal analysis. **William Rowles:** Project administration, Formal analysis. **Kira Mcpolin:** Project administration. **Collin Spencer:** Formal analysis. **Sharon Sagan:** . **Chloe Gerungan:** . **Michael R. Wilson:** . **Scott S. Zamvil:** . **Riley Bove:** . **Joseph J. Sabatino:** Conceptualization, Project administration, Formal analysis. **Tobias Sejbaek:** Conceptualization, Project administration, Formal analysis.

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References

Abbott. *SARS-CoV-2 IgG II Quant for the use with Alinity i*. April 2021 2021.

Achiron, A., Mandel, M., Dreyer-Alster, S., et al., 2021. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther Adv Neurol Disord 14. https://doi.org/10.1177/17562864211012835, 1756286421101283521/05/27.

Addetia, A., Crawford, K.H.D., Dingens, A., et al., 2020. Neutralizing Antibodies Correlate with Protection from SARS-CoV-2 in Humans during a Fishery Vessel Outbreak with a High Attack Rate. J. Clin. Microbiol. 58. https://doi.org/10.1128/jcm.02107-20, 2020/08/23.

Ammitzbøll, C., Bartels, L.E., Bøgh Andersen, J., et al., 2021. Impaired Antibody Response to the BNT162b2 Messenger RNA Coronavirus Disease 2019 Vaccine in Patients With Systemic Lupus Erythematosus and Rheumatoid Arthritis. ACR Open Rheumatol. https://doi.org/10.1002/acr2.11299, 2021/07/18.

Bachiller-Corral, J., Boteanu, A., Garcia-Villanueva, M.J., et al., 2021. Risk of Severe COVID-19 Infection in Patients With Inflammatory Rheumatic Diseases. J. Rheumatol. 48, 1098–1102. https://doi.org/10.3899/jrheum.200755, 2021/03/17.

Baden, L.R., El Sahly, H.M., Essink, B., et al., 2021. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N. Engl. J. Med. 384, 403–416. https://doi.org/10.1056/NEJMoa2035389, 2020/12/31.

Baker, D., Roberts, C.A.K., Pryce, G., et al., 2020. COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. Clin. Exp. Immunol. 202, 149–161. https://doi.org/10.1111/cei.13495, 2020/07/17.

Bar-Or, A., Calkwood, J.C., Chognot, C., et al., 2020. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: The VELOCE study. Neurology 95, e1999–e2008. https://doi.org/10.1212/wnl.0000000000010380, 2020/07/31.

Benotmane, I., Gautier, G., Perrin, P., et al., 2021. Antibody Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Kidney Transplant Recipients With Minimal Serologic Response to 2 Doses. JAMA. https://doi.org/10.1001/jama.2021.12339.

Boyarsky, B.J., Werbel, W.A., Avery, R.K., et al., 2021a. Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients. JAMA 325, 1784–1786. https://doi.org/10.1001/jama.2021.4385.

Boyarsky, B.J., Werbel, W.A., Avery, R.K., et al., 2021b. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA 325, 2204–2206. https://doi.org/10.1001/jama.2021.7489.

Day, A.L., Winthrop, K.L., Curtis, J.R, 2020. The effect of disease-modifying antirheumatic drugs on vaccine immunogenicity in adults. Cleve. Clin. J. Med. 87, 695–703. https://doi.org/10.3949/ccjm.87a.20056, 2020/11/04.

Ebinger, J.E., Fert-Bober, J., Printsev, I., et al., 2021. Antibody responses to the BNT162b2 mRNA vaccine in individuals previously infected with SARS-CoV-2. Nat. Med. 27, 981–984. https://doi.org/10.1038/s41591-021-01325-6, 2021/04/03.

EMA, 2018. *Ocrevus: Summary of Product characteristics*. 2018. European Medicines Agency.

Feng, S., Phillips, D.J., White, T., et al., 2021. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. medRxiv. https://doi.org/10.1101/2021.06.21.21258528, 2021.2006.2021.21258528.

Friedli, C., Diem, L., Hammer, H., et al., 2021. Negative SARS-CoV2-antibodies after positive COVID-19-PCR nasopharyngeal swab in patients treated with anti-CD20 therapies. Ther Adv Neurol Disord 14. https://doi.org/10.1177/17562864211016641, 17562864211016641. 2021/05/29.

Gaitzsch, E., Passerini, V., Khatamzas, E., et al., 2021. COVID-19 in Patients Receiving CD20-depleting Immunochemotherapy for B-cell Lymphoma. Hemasphere 5, e603. https://doi.org/10.1097/hs9.0000000000000603, 2021/07/09.

Kamar, N., Abravanel, F., Marion, O., et al., 2021. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. New England J. Med. https://doi.org/10.1056/NEJMc2108861.

Khoury, D.S., Cromer, D., Reynaldi, A., et al., 2021. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat. Med. https://doi.org/10.1038/s41591-021-01377-8, 2021/05/19.

Killestein, J., Du Pasquier, R., Hemmer, B, 2020. Vaccination in B-cell-depleted patients with multiple sclerosis. Neurology 95, 613–614. https://doi.org/10.1212/wnl.0000000000010378, 2020/07/31.

Kristiansen, P.A., Page, M., Bernasconi, V., et al., 2021. WHO International Standard for anti-SARS-CoV-2 immunoglobulin. Lancet 397, 1347–1348. https://doi.org/10.1016/s0140-6736(21)00527-4, 2021/03/27.

Loarce-Martos, J., García-Fernández, A., López-Gutiérrez, F., et al., 2020. High rates of severe disease and death due to SARS-CoV-2 infection in rheumatic disease patients treated with rituximab: a descriptive study. Rheumatol. Int. 40, 2015–2021. https://doi.org/10.1007/s00296-020-04699-x, 2020/09/19.

Louapre, C., Ibrahim, M., Maillart, E., et al., 2021. Anti-CD20 therapies decrease humoral immune response to SARS-CoV-2 in patients with multiple sclerosis or neuromyelitis optica spectrum disorders. J. Neurol., Neurosurg. Psych. https://doi.org/10.1136/jnnp-2021-326904 jnnp-2021-326904.

Maneikis, K., Šablauskas, K., Ringelevičiūtė, U., et al., 2021. Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective cohort study. Lancet Haematol. 8, e583–e592. https://doi.org/10.1016/s2352-3026(21)00169-1, 2021/07/06.

Nguyen, M.T.T., Lindegaard, H., Hendricks, O., et al., 2017. Initial Serological Response after Prime-boost Pneumococcal Vaccination in Rheumatoid Arthritis Patients: results of a Randomized Controlled Trial. J. Rheumatol. 44, 1794–1803. https://doi.org/10.3899/jrheum.161407, 2017/10/03.

Polack, F.P., Thomas, S.J., Kitchin, N., et al., 2020. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N. Engl. J. Med. 383, 2603–2615. https://doi.org/10.1056/NEJMoa2034577, 2020/12/11.

Rolfes, L., Pawlitzki, M., Pfeuffer, S., et al., 2021. Ocrelizumab Extended Interval Dosing in Multiple Sclerosis in Times of COVID-19. Neurology - Neuroimmunology Neuroinflammation 8, e1035. https://doi.org/10.1212/NXI.0000000000001035.

Sahin, U., Muik, A., Vogler, I., et al., 2021. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature 595, 572–577. https://doi.org/10.1038/s41586-021-03653-6, 2021/05/28.

Salter, A., Fox, R.J., Newsome, S.D., et al., 2021. Outcomes and Risk Factors Associated With SARS-CoV-2 Infection in a North American Registry of Patients With Multiple Sclerosis. JAMA Neurol. 78, 699–708. https://doi.org/10.1001/jamaneurol.2021.0688.

Sormani, M.P., De Rossi, N., Schiavetti, I., et al., 2021. Disease-Modifying Therapies and Coronavirus Disease 2019 Severity in Multiple Sclerosis. Ann. Neurol. 89, 780–789. https://doi.org/10.1002/ana.26028, 2021/01/23.

Teunissen, C.E., Petzold, A., Bennett, J.L., et al., 2009. A consensus protocol for the standardization of cerebrospinal fluid collection and biobanking. Neurology 73, 1914–1922. https://doi.org/10.1212/WNL.0b013e3181c47cc2, 2009/12/02.

Thakkar, A., Gonzalez-Lugo, J.D., Goradia, N., et al., 2021. Seroconversion rates following COVID-19 vaccination among patients with cancer. Cancer Cell. https://doi.org/10.1016/j.ccell.2021.06.002.

Vishnevetsky, A., Hawkes, C., Lechner-Scott, J., et al., 2021. B cell therapy and the use of RNA-based COVID-19 vaccines. Mult Scler Relat Disord 49, 102887. https://doi.org/10.1016/j.msard.2021.102887, 2021/04/23.

Walsh, E.E., Frenck, R.W., Falsey, A.R., et al., 2020. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N. Engl. J. Med. 383, 2439–2450. https://doi.org/10.1056/NEJMoa2027906.

Werbel, W.A., Boyarsky, B.J., Ou, M.T., et al., 2021. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. Ann. Intern. Med. https://doi.org/10.7326/l21-0282, 2021/06/15.