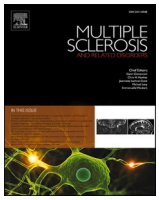
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Multiple Sclerosis and Related Disorders 55 (2021) 103203

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Understanding the impacts of COVID-19 pandemic in people with multiple sclerosis treated with ocrelizumab

A B S T R A C T

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to major challenges in the therapeutic management of patients living with multiple sclerosis (PLwMS), particularly regarding the use of disease-modifying therapies. Despite an extraordinary scientific effort to study SARS-CoV-2 in PLwMS, the heterogeneity of COVID-19 manifestations, immunological mechanisms induced by the natural infection or the vaccines, and the extent of protection through the vaccines, major knowledge gaps remain. Here, we describe the scientific evidence generation plan developed by Roche/Genentech to better understand the impact of the COVID-19 pandemic in PLwMS treated with the B-cell depleting monoclonal antibody ocrelizumab.

The first patient living with multiple sclerosis (PLwMS) treated with ocrelizumab who developed COVID-19 was reported in April 2020 (Novi et al., 2020). He was a 58-year-old white man, with an Expanded Disability Status Scale (EDSS) score of 6.0, diagnosed with primary progressive multiple sclerosis (PPMS) in 2009. Prior to ocrelizumab treatment every 6 months starting in January 2018, he had received interferon beta-1a, glatiramer acetate, and fingolimod. The patient, who had a positive PCR test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was hospitalized for three days. A chest X-ray showed no infiltrations nor other signs of pneumonia, and arterial blood gas test showed normal oxygenation. The patient was treated with symptomatic therapy for fever (paracetamol), with a complete remission of symptoms within two days.

At the time of this first case report, the pandemic had only just been declared. Little was known about the new SARS-CoV-2, coronavirus disease-19 (COVID-19), or immune responses against this new virus, including whether an immune memory would develop following infection, which may confer protection against subsequent infections. Since then, with a few hundred thousand articles published, a wealth of knowledge has been generated at an unprecedented speed. Nevertheless, it is still unknown why, in the general population, some individuals have a mild or asymptomatic disease course, whereas others develop severe manifestations and even fatal outcomes.

This uncertainty is more significant for individuals on immunosuppressive treatments, including patients on B-cell depleting therapies. Ocrelizumab is a humanized anti-CD20 monoclonal antibody approved for the treatment of relapsing MS (RMS) and PPMS. It depletes peripheral CD20+ B cells, while preserving the capacity for B-cell reconstitution and pre-existing humoral immunity (Hauser et al., 2017; Montalban et al., 2017).

Safety is of high importance in MS treatment, and understanding the potential risks for patients treated with ocrelizumab during this pandemic has been a priority from the start. The majority of ocrelizumab-treated patients who became infected with SARS-CoV-2 developed a mild-to-moderate disease course without hospitalization (Hughes et al., 2021; Louapre et al., 2020; Sormani et al., 2021), with risk factors for severe COVID-19 in line with those reported in the general population, including older age, and comorbidities such as obesity, diabetes, hypertension, coronary heart disease, chronic pulmonary or kidney disease, and cancer (Hauser et al., 2021). However, there were also PLwMS treated with ocrelizumab who experienced severe or even fatal disease. Despite what we have learned about the importance of age and comorbidities associated with more severe presentations of COVID-19, the reasons for the dramatic variability in COVID-19 presentations are yet not understood, neither in ocrelizumab-treated patients nor in the general population.

By the end of November 2020, 613 COVID-19 reports out of the over 200,000 PLwMS treated worldwide with ocrelizumab had been received from the post-marketing pharmacovigilance source in the Roche/Genentech Global Safety Database, in addition to 193 reports out of 3,974 patients being treated in unblinded Roche/Genentech clinical studies (Hauser et al., 2021).

In the attempt to provide PLwMS treated with ocrelizumab and the wider MS community with the answers they need, we developed an evidence generation plan around three main scientific questions:

1) Are people treated with ocrelizumab at a higher risk of developing COVID-19, or at higher risk for severe COVID-19?
2) What is the impact of ocrelizumab on the immune response against the virus?
3) Are vaccines administered to patients receiving ocrelizumab eliciting a protective immune response sufficient to provide protection against COVID-19 and severe COVID-19?

The following section details our scientific evidence generation strategy.

1. COVID-19 risk and severity

In the urgency of the pandemic, the MS community has drawn on real-world evidence to study the severity and risk factors for COVID-19 in PLwMS, to understand how and why different populations contracted the disease, the outcomes, and how those vary based on their underlying comorbidities and other factors (MS type, disability or type of disease-

https://doi.org/10.1016/j.msard.2021.103203
Received 9 July 2021; Received in revised form 23 July 2021; Accepted 5 August 2021
Available online 8 August 2021

modifying therapies [DMTs]). Among the breadth of real-world data sources, several registries and data-sharing initiatives have been implemented to study COVID-19 in PLwMS (e.g., without claim of completeness, the Italian MuSC-19 [Sormani et al., 2021], the French registry CoViSEP [Louapre et al., 2020], the North American CoViMS [Salter et al., 2021], and the MS Data Alliance Global Data Sharing Initiative [Peeters et al., 2020]). Studies using electronic health records (EHR) or health insurance claims databases have also emerged (Kovvuru et al., 2021).

As described in Table 1, to better understand risk factors for COVID-19 and disease severity in patients treated with ocrelizumab, we have undertaken a number of initiatives using: **i.** internal sources such as pharmacovigilance data from the post-marketing setting and clinical trials; **ii.** US healthcare databases (EHR linked to claims data); and **iii.** collaborative prospective studies with academic centers. The strengths of pharmacovigilance data from the post-marketing setting and clinical trial data sources include a broad pool of reporters, global coverage, standardized adverse event (AE) reporting, systematic assessment of seriousness and severity grading of AEs, and follow-up of cases with missing information. However, AE reporting is voluntary and post-marketing pharmacovigilance reports often provide incomplete information. There is commonly a reporting bias for more significant outcomes, which may result in an overrepresentation of more severe cases (Hughes et al., 2021). For example, positive PCR in asymptomatic patients is usually not reported as an AE and no testing has been mandated in our clinical trials. These factors may help to contextualize the variability in case fatality rates for ocrelizumab-treated patients observed across registry data (ranging from 0/38 [Louapre et al., 2020] and 1/89 (1.1%) [Sormani et al., 2021] up to 11/484 (2.3%) [Salter et al., 2021]), US EHR database 1/48 (2.1%) (Hughes et al., 2021), and that reported from our post-marketing data 17/307 (5.5%) and clinical trials 3/51 (5.9%) (Hughes et al., 2021). Note that overlap between these data sources cannot be excluded. Studies implemented in collaboration with centers in the US and Switzerland will further explore the clinical course and outcomes of COVID-19 across DMTs in real-world cohorts of patients with MS established prior to the pandemic. Our analyses using EHR linked to claims data will investigate clinical risk factors for COVID-19 in PLwMS. Commitment to continue understanding COVID-19 clinical course in vaccinated versus non-vaccinated ocrelizumab-treated patients will continue in the post-vaccination era.

2. Immunity to SARS-CoV-2

Although the immune correlates of protection against SARS-CoV-2 are not yet fully elucidated, broad evidence suggests that cell-based immunity (CD4+ T cells, CD8+ T cells) (Tan et al., 2021), in addition to neutralizing antibodies (Lucas et al., 2021) contributes to the control of SARS-CoV-2 in both non-hospitalized and hospitalized cases of COVID-19 (Sette and Crotty, 2021). While antibodies play a role in viral clearance and preventing infection, successful recovery from COVID-19 is also observed in individuals with undetectable or low antibody titers (Gallais et al., 2021; Nelde et al., 2021). In addition, the correlation between antibody titers and COVID-19 severity is still controversial and the absence of antibodies, the serum titers of which vary over time, appears not to translate into absence of immunity (Rydyznski Moderbacher et al., 2020; Sette and Crotty, 2021).

Early in the pandemic, concerns were raised regarding the effect of immunosuppressive or immunomodulatory agents, the mainstay treatment for MS, on the antiviral response of PLwMS. Given the B-cell depleting effect of ocrelizumab, understanding how ocrelizumab may affect the development of SARS-CoV-2-specific immune responses following infection or vaccination is of particular importance. Attenuated or even undetectable antibody responses in patients treated with ocrelizumab following SARS-CoV-2 infection have been reported (Conte, 2021). These results are not unexpected given the mechanism of action of ocrelizumab. Moreover, T-cell responses against SARS-CoV-2 appeared not to be affected by anti-CD20 treatment in an initial report (Asplund Högelin et al., 2021).

We are collaborating with several academic partners with the common goal of characterizing the immune response against SARS-CoV-2 following infection in PLwMS treated with ocrelizumab (Table 1). Using both gold-standard methodologies and cutting-edge technologies to assess antibody and T-cell responses, we aim to get clarity on the impact of ocrelizumab on the quantity, quality, and longevity of the immune response against SARS-CoV-2, and potential influence of time on ocrelizumab or time since last infusion.

Preliminary data suggest that PLwMS receiving ocrelizumab develop an immune response (antibodies and/or T cells) against SARS-CoV-2 that persisted up to more than nine months after infection in some patients (Kister et al., 2021). Anti-SARS-CoV-2 antibodies were detected in 58% of the patients receiving ocrelizumab and 97% in patients receiving other DMTs (as determined with Elecsys anti-SARS-CoV-2 assay), and neutralizing antibodies (using a live virus assay) were detectable in 62% of the patients receiving ocrelizumab and 84% of patients treated with other DMTs, although at lower titers in ocrelizumab-treated patients. Since the biological role of anti-SARS-C>oV-2 antibodies is yet to be fully understood, the clinical significance of these preliminary findings remains to be elucidated. Importantly, functional SARS-CoV-2-specific T cells, producing the cytokines interferon-γ and interleukin-2, were detected (by T-cell ELISpot) in more than 80% of ocrelizumab-treated patients and did not differ from those detected in PLwMS treated with other DMTs. Further results from this study and from other collaborative studies will be published once available.

3. COVID-19 vaccination

The development of a protective immune response following vaccination involves multiple mechanisms in which T and B cells are variably involved (Sette and Crotty, 2021). As discussed in a recent editorial in this journal (Vishnevetsky et al., 2021), understanding the relative contributions of humoral and cellular immunity to the protective response elicited by COVID-19 vaccines will help guide management decisions in patients receiving anti-CD20 therapies such as ocrelizumab. Several COVID-19 vaccines, including the mRNA vaccine BNT162b2, elicit robust antibody and T-cell responses (Sahin et al., 2020). Vaccine-induced neutralizing antibody titers were found to be predictive of immune protection from symptomatic infection (Khoury et al., 2021). However, antibodies may not be strictly necessary for protection (Vishnevetsky et al., 2021), as observed by the early efficacy 12 days after one dose of BNT162b2 (Polack et al., 2020), when neutralizing antibodies are still not detected (Sahin et al., 2020). This may be explained, at least in part, by the robust T-cell response induced after one dose of BNT162b2 (Kalimuddin et al., 2021).

Data from our Phase III studies show that pre-existing humoral immunity is not affected by ocrelizumab treatment (Ziemssen et al., 2017). In a recent vaccination study (VELOCE), PLwMS treated with ocrelizumab were able to produce a protective antibody response, albeit attenuated, to various (non-COVID-19) non-live vaccines and the neo-antigen keyhole limpet hemocyanin (Bar-Or et al., 2020). Other immune responses, such as cellular responses, were not investigated in VELOCE and remain an important unanswered question. Therefore, the priority in our COVID-19 evidence generation plan is to provide a comprehensive assessment of both cellular (namely T cells) and humoral immunity induced by COVID-19 vaccines. Antibody responses to COVID-19 vaccines may be attenuated in ocrelizumab-treated patients, as recently shown (Achiron et al., 2021; Guerrieri et al., 2021); however, as discussed above, this may not translate into a lack of efficacy, in particular against severe disease (Vishnevetsky et al., 2021), given that ocrelizumab is not expected to affect other immune components elicited by these vaccines. Indeed, evidence is emerging that PLwMS treated with anti-CD20 generate T-cell responses (CD4 and CD8) after COVID-19 mRNA vaccination (Apostolidis et al., 2021).

Table 1
Summary of Roche/Genentech evidence generation plan for COVID-19 in PLwMS treated with ocrelizumab

Data sources / Studies	Country	Total number of studied subjects/ patients on OCR	COVID-19 risk	COVID-19 severity	SARS-CoV-2 immunity (natural infection)		SARS-CoV-2 vaccine immunity		
					Antibody	Cellular	Safety/ clinical effectiveness	Antibody + cellular immune responses	Vaccine platform
Roche clinical study database	Multiple countries	3,974 on OCR		√			√ [a]		Any locally approved[e]
Post-marketing pharmacovigilance: Global Roche/Genentech Safety Database	Worldwide	Potential ~200,000 on OCR		√			√ [a]		Any locally approved[e]
Primary data collection Non-interventional Studies	Europe, Middle East, LatAm	~4,300 on OCR		√			√ [a]		Any locally approved[e]
Optum Market Clarity	USA	~53,000 MS / ~4,000 on OCR	√	√			√		Any locally approved[e]
COVID-19 MS registry + multiple MS centers	Italy	Over 2,500 MS /over 250 on OCR[b]	√	√	√ [f]	√ [f]			
Single MS center	USA	800 MS/~250 on OCR	√	√	√	√ [f]		√ [d]	Pfizer, Moderna, J&J
Swiss MS cohort	Switzerland	1,400 MS /over 200 on OCR	√	√	√				
Vaccine immune response assessment within Roche trials (ENSEMBLE, CONSONANCE, LIBERTO)	Multiple countries	200–300 on OCR[c]					√	√	Any locally approved[e]
Six collaborations with academic partners	Germany, Israel, Italy, Switzerland, USA	Estimated total of over 400 patients on OCR; with healthy controls and patients on other DMTs						All assess both antibody and cellular responses	Any locally approved (mainly Pfizer, Moderna, J&J, AZ)

AE, adverse event; AZ, AstraZeneca; COVID-19, coronavirus disease 2019; DMT, disease-modifying therapy; J&J, Johnson and Johnson; LatAm, Latin America; MS, multiple sclerosis; OCR, ocrelizumab; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] In clinical study database, data on vaccination are collected as concomitant medication + AE reporting for COVID-19 in all Roche studies.

[b] Approximate number of COVID-19 patients in Italian registry and MS centers as of June 15, 2021.

[c] Planned to enroll up to 300 patients on ocrelizumab depending on feasibility.

[d] The study on natural infection to SARS-CoV-2 has been recently amended to include 120–200 patients on ocrelizumab receiving vaccination with Pfizer, Moderna, or J&J.

[e] All types of SARS-CoV-2 vaccine that will be administered to patients with MS in therapy receiving ocrelizumab as per local national guidelines.

[f] Immunology analysis will be conducted in a subset of patients.

To this end, we have initiated an exploratory vaccination objective in three global Phase IIIb/IV ocrelizumab studies in which consenting patients will take part in blood analyses at various time points before and after vaccination Table 1). We aim to shed light on the effect of ocrelizumab on different arms of the immune response elicited by vaccines, the longevity of the response, the potential impact of time since last ocrelizumab infusion with respect to vaccination, the potential impact of ocrelizumab therapy duration, and the potential variability of immune responses elicited by the multiple vaccine platforms.

In addition, we have partnered with centers around the world in multiple collaborations to study T-cell responses as well as antibody responses to various COVID-19 vaccines (Table 1). Through these scientific collaborations, we hope to provide the MS community with a better understanding of the immune response following COVID-19 vaccines in PLwMS treated with ocrelizumab. A better understanding of the potential effects of timing of COVID-19 vaccination relative to ocrelizumab infusion schedule, also planned in these studies, may also provide treatment strategy elements for the community that wishes to continue to control MS as best as possible, while reaching levels of COVID-19 immunity that are deemed satisfactory. In this regard, information on characteristics of any potential COVID-19 infections post-vaccination will be also monitored in the above-mentioned studies.

In conclusion, major questions regarding clinical outcomes of COVID-19 and the immune response to SARS-CoV-2 and to COVID-19 vaccines in PLwMS treated with ocrelizumab remain unanswered. The evidence generation plan described here will help the MS community to address these important questions and increase the understanding of the impact of COVID-19 on PLwMS treated with ocrelizumab, with new data planned to be released as soon as they become available.

References

Achiron, A., Mandel, M., Dreyer-Alster, S., Harari, G., Magalashvili, D., Sonis, P., Dolev, M., Menascu, S., Flechter, S., Falb, R., Gurevich, M., 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, 17562864211012835.

Apostolidis, S.A., Kakara, M., Painter, M.P., Goel, R.R., Mathew, D., Lenzi, K., Rezk, A., Patterson, K.R., Espinoza, D.A., Kadri, J.C., Markowitz, D.M., Markowitz, C., Mexhitaj, P., Jacobs, D., Babb, A., Betts, M.R., Luning Prak, E.T., Weiskopf, D., Grifoni, A., Lundgreen, K.A., Gouma, S., Sette, A., Bates, P., Hensley, S.E., Greenplate, A.R., Wherry, E.J., Li, R., Bar-Or, A., 2021. Altered cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. medRxiv 2021.06.23.21259389; 10.1101/2021.06.23.21259389.

Asplund Högelin, K., Ruffin, N., Pin, E., Månberg, A., Hober, S., Gafvelin, G., Grönlund, H., Nilsson, P., Khademi, M., Olsson, T., Piehl, F., Al Nimer, F., 2021. Development of humoral and cellular immunological memory against SARS-CoV-2 despite B-cell depleting treatment in multiple sclerosis. Available at SSRN: https://ssrn.com/abstract=3796531 or https://doi.org/10.2139/ssrn.3796531.

Bar-Or, A., Calkwood, J.C., Chognot, C., Evershed, J., Fox, E.J., Herman, A., Manfrini, M., McNamara, J., Robertson, D.S., Stokmaier, D., Wendt, J.K., Winthrop, K.L., Traboulsee, A., 2020. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: The VELOCE study. Neurology 95 (14), e1999–e2008.

Conte, W.L., 2021. Attenuation of antibody response to SARS-CoV-2 infection in patients with multiple sclerosis on ocrelizumab: A case-control study. Mult. Scler. Relat. Disord. 52, 103014.

Gallais, F., Velay, A., Nazon, C., Wendling, M.J., Partisani, M., Sibilia, J., Candon, S., Fafi-Kremer, S., 2021. Intrafamilial exposure to SARS-CoV-2 associated with cellular immune response without seroconversion, France. Emerg. Infect. Dis. 27 (1), 113–121.

Guerrieri, S., Lazzarin, S., Zaentta, C., Nozzolillo, A., Filippi, M., Moiola, L., 2021. Serological response to SARS-CoV-2 vaccination in multiple sclerosis patients treated with fingolimod or ocrelizumab: An initial real-life experience. J. Neurol. Epub ahead of print. https://doi.org/10.1007/s00415-021-10663-x.

Hauser, S.L., Bar-Or, A., Comi, G., Giovannoni, G., Hartung, H.P., Hemmer, B., Lublin, F., Montalban, X., Rammohan, K.W., Selmaj, K., Traboulsee, A., Wolinsky, J.S., Arnold, D.L., Klingelschmitt, G., Masterman, D., Fontoura, P., Belachew, S., Chin, P., Mairon, N., Garren, H., Kappos, L., OPERA I and OPERA II Clinical Investigators, 2017. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N. Engl. J. Med. 376 (3), 221–234.

Hauser, S., Gold, R., Cutter, G., Schneble, H., Whitley, L., Jessop, N., 2021. COVID-19 risk factors in people with multiple sclerosis treated with ocrelizumab. OPR-206. Eur. J. Neurol. 28 (Suppl. 1), 955.

Hughes, R., Whitley, L., Fitovski, K., Schneble, H.M., Muros, E., Sauter, A., Craveiro, L., Dillon, P., Bonati, U., Jessop, N., Pedotti, R., Koendgen, H., 2021. COVID-19 in ocrelizumab-treated people with multiple sclerosis. Mult. Scler. Relat. Disord. 49, 102725.

Kalimuddin, S., Tham, C.Y.L., Qui, M., de Alwis, R., Sim, J.X.Y., Lim, J.M.E., Tan, H.C., Syenina, A., Zhang, S.L., Le Bert, N., Tan, A.T., Leong, Y.S., Yee, J.X., Ong, E.Z., Ooi, E.E., Bertoletti, A., Low, J.G., 2021. Early T cell and binding antibody responses are associated with COVID-19 RNA vaccine efficacy onset. Med. (N Y) 2 (6), 682–688 e4.

Khoury, D.S., Cromer, D., Reynaldi, A., Schlub, T.E., Wheatley, A.K., Juno, J.A., Subbarao, K., Kent, S.J., Triccas, J.A., Davenport, M.P., 2021. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat. Med. 27 (7), 1205–1211. https://doi.org/10.1038/s41591-021-01377-8.

Kister, I., Krogsgaard, M., Mulligan, M.J., Patskovsky, Y., Voloshyna, I., Ferstler, N., Zhovtis Ryerson, L., Curtin, R., Kim, J., Tardio, E., Rimler, Z., Sherman, K., Samanovic-Golden, M., Cornelius, A., Lieberman, D., Solis, S., Pedotti, R., Raposo, C., Priest, J., Hawker, K., Silverman, G.J., 2021. Preliminary results of ongoing, prospective study of antibody and T cell responses to SARS-CoV-2 in patients with MS on ocrelizumab or other disease modifying therapies. P15.014. Neurology 96 (22), e2783–e2784. https://doi.org/10.1212/WNL.0000000000012044.

Kovvuru, S., Nalleballe, K., Onteddu, S.R., Sharma, R., Jasti, M., Kapoor, N., Veerapaneni, K., Yadala, S., Dandu, V., Archer, R., Nowak, R.J., Roy, B., 2021. Immunosuppression in chronic autoimmune neurological disorders during the COVID-19 pandemic. J. Neurol. Sci. 420, 117230.

Louapre, C, Collongues, N., Stankoff, B., Giannesini, C., et al., 2020. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. JAMA Neurol. 77 (9), 1079–1088.

Lucas, C., Klein, J., Sundaram, M.E., Liu, F., Wong, P., Silva, J., Mao, T., Oh, J.E., Mohanty, S., Huang, J., Tokuyama, M., Lu, P., Venkataraman, A., Park, A., Israelow, B., Vogels, C.B.F., Muenker, M.C., Chang, C.H., Casanovas-Massana, A., Moore, A.J., Zell, J., Fournier, J.B., Yale, I.R.T., Wyllie, A.L., Campbell, M., Lee, A.I., Chun, H.J., Grubaugh, N.D., Schulz, W.L., Farhadian, S., Cruz, Dela, C., Ring, A. M., Shaw, A.C., Wisnewski, A.V., Yildirim, I., Ko, A.I., Omer, S.B., Iwasaki, A., 2021. Delayed production of neutralizing antibodies correlates with fatal COVID-19. Nat. Med. 27 (7), 1178–1186. https://doi.org/10.1038/s41591-021-01355-0.

Montalban, X., Hauser, S.L., Kappos, L., Arnold, D.L., Bar-Or, A., Comi, G., de Seze, J., Giovannoni, G., Hartung, H.P., Hemmer, B., Lublin, F., Rammohan, K.W., Selmaj, K., Traboulsee, A., Sauter, A., Masterman, D., Fontoura, P., Belachew, S., Garren, H., Mairon, N., Chin, P., Wolinsky, J.S., ORATORIO Clinical Investigators, 2017. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N. Engl. J. Med. 376 (3), 209–220.

Nelde, A., Bilich, T., Heitmann, J.S., Maringer, Y., Salih, H.R., Roerden, M., Lubke, M., Bauer, J., Rieth, J., Wacker, M., Peter, A., Horber, S., Traenkle, B., Kaiser, P.D., Rothbauer, U., Becker, M., Junker, D., Krause, G., Strengert, M., Schneiderhan-Marra, N., Templin, M.F., Joos, T.O., Kowalewski, D.J., Stos-Zweifel, V., Fehr, M., Rabsteyn, A., Mirakaj, V., Karbach, J., Jager, E., Graf, M., Gruber, L.C., Rachfalski, D., Preuss, B., Hagelstein, I., Marklin, M., Bakchoul, T., Gouttefangeas, C., Kohlbacher, O., Klein, R., Stevanovic, S., Rammensee, H.G., Walz, J.S., 2021. SARS-CoV-2-derived peptides define heterologous and COVID-19-induced T cell recognition. Nat. Immunol. 22 (1), 74–85.

Novi, G., Mikulska, M., Briano, F., Toscanini, F., Tazza, F., Uccelli, A., Inglese, M., 2020. COVID-19 in a MS patient treated with ocrelizumab: Does immunosuppression have a protective role? Mult. Scler. Relat. Disord. 42, 102120.

Peeters, L.M., Parciak, T., Walton, C., Geys, L., Moreau, Y., De Brouwer, E., Raimondi, D., Pirmani, A., Kalincik, T., Edan, G., Simpson-Yap, S., De Raedt, L., Dauxais, Y., Gautrais, C., Rodrigues, P.R., McKenna, L., Lazovski, N., Hillert, J., Forsberg, L., Spelman, T., McBurney, R., Schmidt, H., Bergmann, A., Braune, S., Stahmann, A., Middleton, R., Salter, A., Bebo, B.F., Rojas, J.I., van der Walt, A., Butzkueven, H., van der Mei, I., Ivanov, R., Hellwig, K., Sciascia do Olival, G., Cohen, J.A., Van Hecke, W., Dobson, R., Magyari, M., Brum, D.G., Alonso, R., Nicholas, R., Bauer, J., Chertcoff, A., de Seze, J., Louapre, C., Comi, G., Rijke, N., 2020. COVID-19 in people with multiple sclerosis: A global data sharing initiative. Mult. Scler. 26 (10), 1157–1162.

Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J.L., Perez Marc, G., Moreira, E.D., Zerbini, C., Bailey, R., Swanson, K.A., Roychoudhury, S., Koury, K., Li, P., Kalina, W.V., Cooper, D., Frenck Jr., R.W., Hammitt, L.L., Tureci, O., Nell, H., Schaefer, A., Unal, S., Tresnan, D.B., Mather, S., Dormitzer, P.R., Sahin, U., Jansen, K.U., Gruber, W.C., Group, C.C.T., 2020. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N. Engl. J. Med. 383 (27), 2603–2615.

Rydyznski Moderbacher, C., Ramirez, S.I., Dan, J.M., Grifoni, A., Hastie, K.M., Weiskopf, D., Belanger, S., Abbott, R.K., Kim, C., Choi, J., Kato, Y., Crotty, E.G., Kim, C., Rawlings, S.A., Mateus, J., Tse, L.P.V., Frazier, A., Baric, R., Peters, B., Greenbaum, J., Ollmann Saphire, E., Smith, D.M., Sette, A., Crotty, S, 2020. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. Cell 183 (4), 996–1012 e1019.

Sahin, U., Muik, A., Derhovanessian, E., Vogler, I., Kranz, L.M., Vormehr, M., Baum, A., Pascal, K., Quandt, J., Maurus, D., Brachtendorf, S., Lorks, V., Sikorski, J., Hilker, R., Becker, D., Eller, A.K., Grutzner, J., Boesler, C., Rosenbaum, C., Kuhnle, M.C., Luxemburger, U., Kemmer-Bruck, A., Langer, D., Bexon, M., Bolte, S., Kariko, K., Palanche, T., Fischer, B., Schultz, A., Shi, P.Y., Fontes-Garfias, C., Perez, J.L., Swanson, K.A., Loschko, J., Scully, I.L., Cutler, M., Kalina, W., Kyratsous, C.A., Cooper, D., Dormitzer, P.R., Jansen, K.U., Tureci, O., 2020. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature 586 (7830), 594–599.

Salter, A., Fox, R.J., Newsome, S.D., Halper, J., Li, D.K.B., Kanellis, P., Costello, K., Bebo, B., Rammohan, K., Cutter, G.R., Cross, A.H., 2021. Outcomes and risk factors associated with SARS-CoV-2 infection in a North American registry of patients with multiple sclerosis. JAMA Neurol. 78 (6), 699–708.

Sette, A., Crotty, S., 2021. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell 184 (4), 861–880.

Sormani, M.P., De Rossi, N., Schiavetti, I., Carmisciano, L., Cordioli, C., Moiola, L., Radaelli, M., Immovilli, P., Capobianco, M., Trojano, M., Zaratin, P., Tedeschi, G., Comi, G., Battaglia, M.A., Patti, F., Salvetti, M., 2021. Musc-19 Study, G., 2021. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. Ann. Neurol. 89 (4), 780–789.

Tan, A.T., Linster, M., Tan, C.W., Le Bert, N., Chia, W.N., Kunasegaran, K., Zhuang, Y., Tham, C.Y.L., Chia, A., Smith, G.J.D., Young, B., Kalimuddin, S., Low, J.G.H., Lye, D., Wang, L.F., Bertoletti, A., 2021. Early induction of functional SARS-CoV-2-specific T cells associates with rapid viral clearance and mild disease in COVID-19 patients. Cell Rep. 34 (6), 108728.

Vishnevetsky, A., Hawkes, C., Lechner-Scott, J., Giovannoni, G., Levy, M., Pohl, D., 2021. B cell therapy and the use of RNA-based COVID-19 vaccines. Mult. Scler. Relat. Disord. 49, 102887.

Ziemssen, T., Bar-Or, A., Arnold, D.L., Comi, G., Hartung, H.P., Hauser, S.L., Lublin, F., Selmaj, K., Traboulsee, A., Chin, P., Fontoura, P., Garren, H., Masterman, D., Kappos, L., 2017. Effect of ocrelizumab on humoral immunity markers in the phase iii, double-blind, double-dummy, IFN-1βa–controlled OPERA I and OPERA II studies. P2. Clin. Neurophys. 128 (10), e326–e327.

Rosetta Pedotti*, Erwan Muros-Le Rouzic, Catarina Raposo, Sven Schippling, Nikki Jessop
F. Hoffmann-La Roche Ltd, Basel, Switzerland

* Corresponding author.
E-mail address: rosetta.pedotti@roche.com (R. Pedotti).