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Commentary

SARS-CoV-2 vaccination in multiple sclerosis: A clearer picture for the time point during CD20 depleting therapy

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The ongoing coronavirus disease 2019 (COVID-19), one of the deadliest pandemics in history, is associated with significant considerations for people living with multiple sclerosis (plwMS). The interest is motivated by knowing that viral infections are triggers for disease exacerbation [1]. In this chronic inflammatory demyelinating disorder of the central nervous system (CNS), relapses associated with infectious stimuli lead to more prolonged and severe clinical worsening than spontaneous relapses [2]. Moreover, plwMS have a higher risk of infections, increased need, and extended stay at the intensive care unit [3]. The likelihood of infections further increases by immunomodulatory and immunosuppressive agents required for adequate disease control in many patients. Admittedly, the impact of COVID-19 on disease reactivation in MS is still under investigation. However, a recent pooled analysis of 18 observational studies comprising 5634 pwMS provides the first evidence for the assumption that plwMS are a vulnerable group for severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection [4]. The study revealed a 24% higher risk of death, an observation that requires confirmation in prospective trials.

Moreover, in a study of 125 plwMS, more than two-thirds developed humoral immunity at a level considered protective after COVID-19 [5]. Notably, the chance of developing SARS-CoV-2 antibodies was halved by the treatment with immunosuppressive therapies, particularly the anti-CD20 monoclonal antibodies rituximab and ocrelizumab. The points mentioned above are only the spearheads for the considerations for effective infection prevention employing vaccination against SARS-CoV-2 in plwMS.

In this issue of EBioMedicine, Sormani et al. report the first results from a large-scale study conducted across 35 MS centers in Italy with the mRNA vaccines BNT162b2 (BioNTech/Pfizer, 76.2%) or mRNA-1273 (Moderna, 23.8%) [6]. Post-vaccination SARS-CoV-2 antibodies were detected in 677 individuals (86.8%). At multivariable analysis, the antibody levels with ocrelizumab (201-fold decrease, $p<0.001$), fingolimod (26-fold reduction, $p < 0.001$), and rituximab treatment (20-fold reduction, $p<0.001$) were significantly lower as compared to patients without a disease-modifying drug (DMD). Furthermore, the antibody titers on ocrelizumab and rituximab, given iv at six-month intervals, correlated to the time since the last infusion, and rituximab had longer intervals (mean 386 days) than that ocrelizumab (mean 386 and 129 days, respectively). Thus, the authors propose a time point of 143 days after the last infusion as the turning point after which a sufficient humoral immune response is mounted. Interestingly, the use of the mRNA-1273 vaccine showed systematically 3.25-fold higher antibody levels than the BNT162b2 vaccine, indicating differences in the immunogenicity of these two mRNA vaccine preparations. None in this cohort was on treatment with ofatumumab, a CD20 depleting monoclonal antibody iven subcutaneously at 4-week intervals. A prolongation of the administration periods may be required to mount an effective immune response on treatment with this DMD.

A key issue is whether the lower and waning antibody levels also yield more (severe) breakthrough infections. While it seems clear that neutralizing antibodies after SARS-CoV-2 vaccination correlates well with protective immunity, the cut-off for antibody-based SARS-CoV-2 threshold remains to be established [7]. In addition, ocrelizumab depletes circulating B cells within two weeks of treatment, while there is a sparing for CD20-negative plasma cells, stem cells, and pro-B cells. Therefore, the resulting impairment in the antibody response shown in this study is not unexpected and is known for non-live vaccines [8].

Moreover, the humoral immune response is only one arm to provide protective immune responses following vaccination. Early and robust T-cell responses are present with mild/asymptomatic COVID-19 infection even in the absence of antibodies. In ocrelizumab-treated

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plwMS, while having lower or absent antibodies levels, SARS-CoV-2 T-cell responses after vaccination with BNT162b2 are comparable to those in healthy individuals [9]. Notably, the original pathogen challenges the immune system with a broad spectrum of antigens and provides a complex and diverse immune response, whereas vaccination likely induces a narrower reaction. There might be differences in the immunogenicity of mRNA vaccines and related to the immunotherapy and the mode of action of the vaccine, with vector-based vaccines yielding even higher seropositivity rates and antibody titers with fingolimod treatment [10]. For fingolimod, a lipophilic S1P analog, the authors of the study mentioned above discuss a potential interaction with mRNA nanoparticles, potentially lessening the integrity and the immune response of mRNA vaccines.

The subsequent steps by Sormani et al. are commendable in that they will try to answer some of the questions raised. The planned increase of the study cohort, additional observational time points at 6 and 18 months, and ideally with heterologous boostering using another mRNA or a vector-based vaccine will demonstrate how antibody levels develop longer-term and remain protective in plwMS treated with DMD.

Contributors

Both authors were equally involved in literature search, design and writing of this commentary.

Declaration of Competing Interest

ECS has no conflicts of interest to report. JS received honoraria for lectures, assembly of teaching material and participation in advisory boards from Alexion, Biogen, BMS/Celgene, Merck, Novartis, Sanofi/Genzyme and Roche.

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References

[1] Steelman AJ. Infection as an environmental trigger of multiple sclerosis disease exacerbation. Front Immunol 2015;6:520.
[2] Marrodan M, Alessandro L, Farez MF, Correale J. The role of infections in multiple sclerosis. Mult Scler 2019;25(7):891–901.
[3] Karamyan A, Dunser MW, Wiebe DJ, Pilz G, Wipfler P, Chroust V, et al. Critical illness in patients with multiple sclerosis: a matched case-control study. PLoS One 2016;11(5):e0155795.
[4] Prosperini L, Tortorella C, Haggiag S, Ruggieri S, Galgani S, Gasperini C. Increased risk of death from COVID-19 in multiple sclerosis: a pooled analysis of observational studies. J Neurol 2021.
[5] Bsteh G, Durauer S, Assar H, Hegen H, Heschl B, Leutmezer F, et al. Humoral immune response after COVID-19 in multiple sclerosis: a nation-wide Austrian study. Mult Scler 2021:13524585211049391.
[6] Sormani MP, Inglese M, Schiavetti I, Carmisciano L, Laroni A, Lapucci C, et al. Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. EBioMedicine 2021:103581.
[7] Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 2021;27(7):1205–11.
[8] Bar-Or A, Calkwood JC, Chognot C, Evershed J, Fox EJ, Herman A, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. Neurology 2020;95(14):e1999–2008.
[9] Brill L, Rechtman A, Zveik O, Haham N, Oiknine-Djian E, Wolf DG, et al. Humoral and T-Cell response to SARS-CoV-2 vaccination in patients with multiple sclerosis treated with ocrelizumab. JAMA Neurol 2021.
[10] Rommer PS, Bsteh G, Berger T, Zettl UK. SARS-CoV-2 antibodies in multiple sclerosis patients depending on the vaccine mode of action? Mult Scler 2021:13524585211039128.