TWO YEARS OF COVID-19 IN THE MS COMMUNITY: WHAT HAVE WE LEARNT SO FAR?

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Two years have elapsed since the beginning of the coronavirus disease-2019 (COVID-19) pandemic. In this time, the international multiple sclerosis (MS) community has tried, through national and international registries, to address a number of important emerging issues. At the beginning of the pandemic, research focused on defining the risk of MS patients, untreated and treated, of being infected with COVID-19 or of having a more severe course. With the introduction of SARS-CoV-2 vaccines, the centre of attention turned to the immunological response to both SARS-CoV-2 infection and vaccines and the way in which disease modifying treatments (DMT) affected these responses. In addition, the publication of many case reports about demyelinating diseases starting short after COVID-19 or SARS-CoV-2 vaccine raised the question of whether this immune response may trigger MS or other central nervous system autoimmune diseases.

During the first year of the pandemic, the results obtained from the COVID-19 and MS cohorts allowed the MS community to assess the risk factors for susceptibility and severity in these patients. Although patients with MS (pwMS) do not seem to be at an increased risk of SARS-CoV-2 infection, factors such an older age, black race, comorbidities, higher disability or a progressive form seem to increase the risk of a severe COVID-19 in pwMS.[1,2] Anti-CD20 therapies were the only DMTs that increased the severity risk in some studies.[2] For example, in Sweden where off-label rituximab is the most common DMT strategy, *Spelman T et al* report 292 confirmed COVID-19 cases with a hospitalization risk of 23.2%. Therefore, rituximab-treated patients present a higher hospitalization rate compared to the combination of all other DMTs (29.9% vs 12.7%).[3]

In view of these facts, some MS centres tried to modify their DMT prescription strategies in order to reduce the risk of severe COVID-19 in those patients with a higher risk.[4] Some favoured other high efficacy treatments such as natalizumab instead of anti-CD20-therapies[5] while others successfully implemented extended-interval dosing of anti-CD20s therapies.[6,7] *Van Lierop ZYGJ et al* personalized ocrelizumab treatment in 159 patients by re-dosing when CD19 B-cell count were over 10 cells/µl. No patients developed relapses and only two (1.9%) had magnetic resonance imaging (MRI) activity.[7]

PwMS and especially those receiving immunosuppressive treatments, have been considered a vulnerable group since the beginning of the pandemic. How pwMS have adapted to the changes and restrictions of the pandemic has also been addressed by researchers. A prospective study performed by *Garjani et al* including 2010 pwMS and comparing them to 380 people without MS found that although pwMS were more likely to present with anxiety and depression during the first surge of the pandemic, the rates did not change during the pandemic compared to the previous year.[8] These results highlight the higher rates of mental health diseases in pwMS compared to the general population and the importance of always optimizing psychological interventions for these patients even in a pandemic scenario.[9]

SARS-CoV-2 vaccine willingness is increased in pwMS compared to the general population probably due to the perceived higher risk of COVID-19. In this sense, *Uhr L and Mateen FJ* evaluated vaccine willingness in 701 pwMS with an online survey. 76.6% of those were COVID-19 vaccine willing, a higher rate than the general population (69%). Vaccine willingness decreased in younger age, racial minorities and higher functional disability.[10] Since some of these factors increase COVID-19 severity in pwMS, public health interventions should be addressed to increase vaccination in these sectors of the population.

As MS is an immune mediated disease and DMTs alter or suppress in different ways the immune system, many recent studies have focused on the immunological responses after SARS-CoV-2 infection or vaccination. Overall, most pwMS present an immunological response after SARS-CoV-2 infection (humoral response: 76.8-83.4%; cellular response: 59.5%)[11–13] or vaccination (humoral response: 74.4-86.8%; cellular response: 62-84.4%)[14–17] regardless of their treatment. However, it is clear by now that anti-CD20 therapies and sphingosine-1-phosphate receptor modulators (SP1RM) therapies decrease these responses.[11,15–18]

Anti-CD20s therapies impair memory B-cell production leading to a blunted humoral response. In the study of *Sormani et al* a SARS-CoV-2 serological response, after COVID-19, was observed in only in 44.6% of patients on anti-CD20 therapies compared to 78.7% of the rest of patients.[11] Similar seroconversion rates are seen after vaccination (40.0-50.0%).[15,17,18] In these patients, seroconversion is highly predicted by B-cell count and time elapsed since last infusion.[14,17,18] Despite the reduction of seroconversion, it remains a robust T cell response after both infection (66.7%)[13] and vaccination (86.4%-92%).[16,17] Therefore, in anti-CD20-treated patients optimizing the moment of vaccine administration could potentially lead to an increased vaccine response.

SP1RM therapies prevent lymphocytes from leaving the lymph nodes. These treatments present an underwhelming vaccination response both in relation to humoral (41-51.4)[15,17] and cellular responses (11.0-14.0%).[16,17] However, immune responses after infection seem to be relatively preserved (66.7-80.0).[11–13] Thus, it is possible that the complexity of the immunological responses after natural infection allows the development of an effective response to the virus as well as a humoral response even in the presence of SP1RM treatment; while post-vaccine immunological responses are much narrower and weaker, blocking the creation of immunological memory.[19]

Probably the most relevant question is whether vaccination prevents severe COVID-19 even in those with blunted vaccine response. This is addressed in several papers, *Januel E et al* report of 18 cases of mild COVID-19 after two doses of BNT162b2-vaccination from the French cohort, 13 of which were treated with anti-CD20 and four with fingolimod.[20] A recent pre-print publication detected 137 breakthrough infections out of 19641 vaccinated pwMS, with significantly higher infection rates in fingolimod and ocrelizumab-treated patients. In this case, the hospitalization rate were higher in

ocrelizumab patients compared to fingolimod or the rest of pwMS (16.7%, 3.6% and 3.9% respectively).[21]

SARS-CoV-2 vaccines have demonstrated to be safe in pwMS and other demyelinating diseases. However, some rare cases of neurological adverse events including new diagnoses of MS, transverse myelitis, acute disseminated encephalomyelitis (ADEM) or MS relapses are being described after all types of SARS-CoV-2 vaccines. *Dams and Rinaldi* describe a myelin oligodendrocyte glycoprotein (MOG)-positive longitudinal extensive transverse myelitis[22] and an ADEM case[23] after ChAdOx1 nCoV-19 vaccine. The association of neurological autoimmunity with infection or vaccination is hypothesized to be due to molecular mimicry or non-specific immune activation but causal relationship is hard to establish and further studies are needed.[24,25] At the current state of knowledge, SARS-CoV-2 vaccination is recommended as COVID-19 risk outweighs the risk of rare vaccine adverse events.

All the manuscripts published in this issue provide remarkable examples of the response of the MS community to address all the gaps of knowledge that COVID-19 has brought us. We have to continue to work together in order to tackle some of the important missing points such as the effect on the immune system of repeated booster vaccines with different types of vaccines and the real effect of treatment on the severity of COVID independent from the concomitant comorbidities.

DECLARATION OF CONFLICTING INTERESTS

A Zabalza has received travel expenses for scientific meetings from Biogen-Idec, Merck Serono and Novartis, speaking honoraria from Eisai and a study grant from Novartis.

AJ Thompson reports personal fees paid to his institution from Eisai Ltd; is an editorial board member for The Lancet Neurology receiving a free subscription; is Editor-in-Chief for Multiple Sclerosis Journal receiving an honorarium from SAGE Publications; receives support for travel as Chair, Scientific Advisory Committee, International Progressive MS Alliance, and from the National MS Society (USA) as member, NMSS Research Programs Advisory Committee.

X Montalban received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Abbvie, Actelion, Alexion, Bayer, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, Medday, Merck, Mylan, Nervgen, Novartis, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF, and NMSS.

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