Q&As from the *triMSx* meeting '**COVID-19** and **MS**: where are we now and where next?' on 8 and 9 April 2021

It should be noted that this information was provided for the *triMSx* meeting on the 8 and 9 April 2021. Given the fast-paced developments with the COVID-19 pandemic, we would advise you to use up-to-date guidance relevant to your own Country.

It should also be noted that this document mentions the use of unlicensed medicines and medicines used outside their indication. Prescribers should consult local prescribing information.

Unfortunately, given the current global situation, not all questions were able to be answered.

Hollie Schmidt

Q. What additional questions are the different research initiatives currently exploring in relation to COVID-19?

A. The MS Data Alliance and the MS International Federation have set up a Global Data Sharing Initiative (GDSI) to explore COVID-19 outcomes in people with MS, with a focus on the impact of MS DMTs on COVID-19 severity:
https://msdataalliance.com/covid-19/covid-19-and-ms-global-data-sharing-initiative/

A pre-print of the initial results from GDSI is available here:
https://www.medrxiv.org/content/10.1101/2021.02.08.21251316v1

The GDSI is now working to identify and map data collection efforts regarding COVID-19 vaccination in people with MS:
https://msdataalliance.com/covid-19/covid-19-vaccines-mapping-exercise/

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One such effort is underway within iConquerMS, a US-based international MS community. This study, called COVER-MS, is aimed at understanding how well the different vaccines work in people with MS through a self-reported survey effort: https://www.iconquerms.org/cover-ms-description

There have also been several explorations of the impact of COVID-19 on access to healthcare and quality of life for people with MS. For instance, iConquerMS and Massachusetts General Hospital conducted a survey of 1000 people on this topic, with results available in this publication: https://www.sciencedirect.com/science/article/pii/S2211034820305873

We are also supporting a study on the utilization of and satisfaction with telemedicine among people with MS and their healthcare providers during the COVID-19 era and look forward to reporting results soon.

Q. What additional data do you hope will emerge from the various vaccine research initiatives?

A. I hope that the data will show that people with MS are well-protected by the available COVID-19 vaccines with no additional safety concerns beyond those found in the general population. But, if there are issues regarding the safety or effectiveness of any of the vaccines in people with MS (including subgroups such as people on certain DMTs), I hope that the data will highlight these issues quickly, so that appropriate actions can be taken to respond to and mitigate them.

I also hope that the various initiatives will continue to collect data into the foreseeable future to help address new topics that emerge, such as the use of booster vaccines in people with MS should these become recommended.

Q. Have you heard of any specific concerns relating to fertility? How can you most effectively combat disinformation about this?

A. Yes, I have heard about this type of concern, and in fact this morning I saw an article in *The Scientist* on the exact topic: https://www.the-scientist.com/news-opinion/no-proof-covid-19-vaccine-affects-menstruation-or-fertility-68720

To combat disinformation, you could share articles like this one. You could also refer people to resources from government agencies who are studying vaccine adverse events, including those in pregnant women. Here is a presentation from the US Centers for Disease Control and Prevention (see page 37 for a summary): https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/28-03-01/05-covid-Shimabukuro.pdf

It includes a statement that “No unexpected pregnancy or infant outcomes have been observed related to COVID-19 vaccination during pregnancy.” It might also be helpful to point out that

pregnant women who contract COVID-19 face a higher risk for severe illness or poor pregnancy outcomes than non-pregnant women, as outlined here: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnant-people.html

Therefore, getting vaccinated against COVID-19 is a good idea for women who are pregnant or considering becoming pregnant.

Professor Klaus Schmierer

Q. Could you give some information about clotting problems with AstraZeneca vaccine? Are they venous thrombosis and pulmonary embolism or arterial diseases?

A. These are venous thromboses and pulmonary embolism, some associated with disseminated intravascular coagulation (DIC). Events clinically mimic autoimmune heparin-induced thrombocytopenia. Check https://pubmed.ncbi.nlm.nih.gov/33835769/

Q. We started cladribine treatment in a patient with highly aggressive MS, she received the second dose mid-March 2021. When is the most appropriate time to give the COVID-19 vaccination?

A. Any time from now. The data from MAGNIFY-MS and CLOCK-MS are reassuring in that patients on cladribine build an effective immune response, even during mild–moderate total lymphocyte depletion.

Q. What are your thoughts on subcutaneous natalizumab?

A. Positive, if used wisely. It will reduce the need to visit the centre, but there needs to be a highly dependable follow-up pathway.

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Associate Professor Liesbet Peeters

Q. How do you see the data science principles that you used in this project being applied to other areas of medicine? Is there a particular disease area you would like to tackle next?

A. The MS Data Alliance focuses solely on MS. However, these data science principles are most definitely of interest for other disease areas. For those who are interested, I refer you to some interesting initiatives that are using similar approaches in other disease areas:

- European Health Data and Evidence Network
- Observational Health Data Sciences and Informatics
- PIONEER
- HONEUR
- European Medical Information Framework
- GAIA-X
- DARWIN-EU
- And so many more…

Q. What is the key factor that has enabled you to aggregate and assess this data so rapidly?

A. The MS community came together as a group within a few days and weeks. There was a very clear and inspiring mission. Therefore, most of the 'sociological' barriers were dropped. I am convinced that this has contributed as a key success factor to speed up this initiative.

Q. We see that you assessed data from 12 sources – is it still possible for new partners to join this initiative? If so, can an individual MS centre sign up, which is not part of a large registry or database?

A. Yes, that is possible! New partners are always welcome. Please reach out to us and we can provide you with more details.

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Q. Is there any relationship between the length of anti-CD20 treatment (months) and higher risk of hospital visits, ICU or worse disease?

A. Until now, we were not able to assess this. The cohort was still too small the last time we did the analyses (December 2020). We aim to redo the analyses soon (June–July) and this will be one of the key research questions we aim to address in this round of analyses.

Professor Ron Milo

Q. New data from Professor Annat Achiron at the Sheba Medical Centre, Israel, has recently revealed the preliminary seroconversion rates in Israeli patients with MS on various DMTs – this is in response to the Pfizer-BioNTech COVID-19 vaccine. As expected, the antibody seroconversion rates in response to anti-CD20 therapies and S1P modulators are blunted and, in most cases, inhibited. Would you like to comment at all on this data or subsequent findings?

A. I have several comments on the Achiron et al. study and claims:

- They tested their antibody level with a kit of unknown validity, probably not the most sensitive one, and I am not sure that it measures antibodies that correlate with neutralizing activity.
- I can't understand their claims that patients on fingolimod should not get vaccinated, or they should have a lymphocyte count >1000 to get an efficient immunization, while they haven't measured or considered cellular immunity that may confer protection, or while their own data show no correlation between lymphocyte count and the ability to mount an antibody response. These claims are against all professional recommendations regarding vaccination in MS patients.
- Our own preliminary results show that about 40% of patients treated with ocrelizumab mount a positive antibody response (albeit lower than with other medications) to the vaccine that is sufficient for immunization, and that most of them have also positive cellular response to the vaccine. A considerable rate of patients on fingolimod also mounted a positive antibody response.

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Q. What recommendation do you give about other anti-CD20 DMTs with a subcutaneous route of administration?

A. It is difficult to give evidence-based advice regarding vaccinating patients on ofatumumab that is administered every 4 weeks. There is no B-cell repletion between doses, and there seems to be no benefit with holding doses or awaiting 2–4 weeks prior to the next dose, which means giving the vaccine right after the previous dose when there are no B cells in the blood. From our experience, patients on ofatumumab develop cellular immunity to the vaccine. Until more data are available, I believe they should get vaccinated (each vaccine to be administrated 2 weeks prior to the next injection of ofatumumab). According to future studies, a third booster vaccine may be required.

Q. Is there any data about how the patient on B-cell therapy developing immunity after vaccination?

A. Only those of Achiron et al. (*Ther Adv Neurol Disord* 2021;14:1–8) or our unpublished data mentioned above.

Q. Do immunosuppressed patients (MS and others) and also patients on anti-CD20 have different proportion of virus strain/mutation than other populations?

A. Not that I know of.

Q. About anti-CD 20 possible dangerous effect on COVID infection, did the multivariate analyses take into account age, EDSS and comorbidities?

A. The studies showing increased rate and severity of COVID-19 in patients treated with anti-CD20 mAbs are not ours, and were published by Italian, French and Iranian groups. However, a study from an American registry has not confirmed this.

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