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COVID-19 prevention and multiple sclerosis management: The SAFE pathway for the post-peak

ABSTRACT

Background: We hereby report on our experience from Naples (South Italy), where the peak of coronavirus disease 2019 (COVID-19) has already passed.

Methods: Assuming that COVID-19 will be circulating until vaccination and/or herd immunity is achieved (possibly not earlier than 2021), we have developed a protocol for the long-term management of multiple sclerosis (MS).

Results: We have defined a pathway for the access to the MS Centre with logistic, preventative and clinical recommendations, and have also included 14-day self-isolation and COVID-19 testing before some disease modifying treatments.

Discussion: Overall, we believe our experience could be helpful for MS management in the upcoming months.

In the last days of December 2019, Wuhan (China) experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 has progressively spread through the world, and, on March 11th, the WHO declared COVID-19 as a pandemic (IHME COVID-19 health service utilization forecasting team, 2020).

People with multiple sclerosis (MS) have immediately been classified as at-risk population, in consideration of higher COVID-19 morbidity and mortality in people with comorbid diseases, and of the use of disease modifying treatments (DMTs) affecting the immune system (Amor et al., 2020; Brownlee et al., 2020). Not least, independently of COVID-19, people with MS are especially at risk of death from respiratory and infectious diseases (Burkill et al., 2017). Accordingly, national and international consensus have suggested to delay/suspend DMTs which cause a pronounced impairment of the immune response (Amor et al., 2020; Brownlee et al., 2020). This recommendation, though certainly necessary in the exponential phases of the epidemic, with healthcare resources and staff being redeployed towards COVID-19 management, holds limitations in the long term (Leocani et al., 2020). Indeed, the use of highly effective DMTs cannot be postponed indefinitely, and, possibly, does not add much risk to MS patients, when compared with general population (Hughes et al., 2020; Montero-Escribano et al., 2020; Sormani and On behalf of the Italian Study Group on COVID-19 infection in multiple sclerosis, 2020).

In the Campania Region (South Italy), the lockdown was enforced on March 9th, when we recorded less than 200 cases over 5.8-million inhabitants. Thus, the curve of the epidemic has been reasonably flat, minimizing the risk of SARS-CoV-2 infection. Thus, our experience will possibly apply to the many countries where the peak of contagion has now passed, but the SARS-CoV-2 is still expected to circulate, at least until a vaccine is available (possibly not earlier than January 2021) and/or herd immunity is achieved (Cohen, 2020).

The key points of our COVID-19-SAFE pathway include:

- SCREEN. All patients are screened for active fever and/or respiratory symptoms with a phone call before attending the MS centre. At the time of the access, patients are again asked about active fever and/or respiratory symptoms and have their body temperature measured with non-contact infrared thermometer. For patients commencing or re-dosing immunosuppressive treatments, serological test for IgG and IgM anti-SARS-CoV-2, and/or oropharyngeal swab for SARS-CoV-2 RT-PCR are performed, as detailed in Table 1.

- ACCESS. Every access is carefully separated from others. Caregivers are not allowed to access the MS Centre, with nurses and porters taking care for the most vulnerable patients.

- FACE. Patients are required to wear, all the time, protective surgical-grade masks, which are deemed to prevent SARS-CoV-2 diffusion (Gandhi et al., 2020). Staff are also required to wear protective surgical-grade masks, though, for prolonged contact procedures (e.g., infusions, lumbar punctures), the staff is using filtering facepiece (FFP)-2 masks and protective goggles or face shields.

- E-Health. In accordance with Italian (and most countries') recommendations, people with MS should self-isolate, by staying at home and reducing the number of contacts with people (Waldman et al., 2020). Thus, as already recommended (Waldman et al., 2020), to avoid unnecessary accesses to the hospital, we have implemented a video-consultation service.
Correspondence

Table 1
Suggested DMT management for COVID-19 prevention.

| Before (re)treatment | Follow-up after (re)treatment |
|----------------------|-------------------------------|
| **Alemtuzumab**      | • SARS-CoV-2 serological testing and/ or oro-pharyngeal swab | • Protective surgical-grade masks |
|                      | • 14-day self-isolation       | • Self-isolation or reduction in social contacts (also accounting for lymphocyte count) |
| **Anti-CD20**

*or rituximab*

|                      | • SARS-CoV-2 serological testing and/ or oro-pharyngeal swab | • Protective surgical-grade masks |
|                      | • 14-day self-isolation       | • Self-isolation or reduction in social contacts (also accounting for lymphocyte count) |
| **Autologous haematopoietic stem cell transplantation** | • SARS-CoV-2 serological testing and/or oro-pharyngeal swab | • Protective surgical-grade masks |
|                      | • 14-day self-isolation       | • Self-isolation or reduction in social contacts (also accounting for lymphocyte count) |
| **Cladribine**       | • SARS-CoV-2 serological testing and/or oro-pharyngeal swab | • Protective surgical-grade masks |
|                      | • 14-day self-isolation       | • Self-isolation or reduction in social contacts (also accounting for lymphocyte count) |
| **Dimethyl fumarate** | • As usual                   | • More frequent FBC if lymphocytes < 800/μL |
| **Glatiramer acetate**| • As usual                   | • Stop if lymphocytes < 500/μL |
| **Interferon-beta**  | • As usual                   | • More frequent FBC if lymphocytes < 500/μL |
| **Natalizumab**      | • As usual                   | • Alternate doses if lymphocytes < 500/μL continuously |
| **S1P inhibitors**

*or siponimod*

|                      | • SARS-CoV-2 serological testing and/or oro-pharyngeal swab | • Stop if lymphocytes < 200/μL |
|                      | • 14-day self-isolation       | • More frequent FBC if lymphocytes < 800/μL |
| **Teriflunomide**    | • As usual                   | • Stop if lymphocytes < 500/μL |

Table shows suggested procedures before treatment (or re-treatment), and during follow-up for different DMTs.

(Moccia et al., 2020b), and have liaised with local services (e.g., family doctors, community services) to deliver healthcare services in the area of residence. For instance, most blood tests and MRIs for DMT monitoring were originally performed at our university hospital, whilst they are now conducted in other facilities, and then online transferred to our servers for review from the treating physician.

Looking at screening and monitoring procedures for people on different DMTs (Table 1), we fully agree with previous recommendations suggesting to carefully balance risks and benefits for delaying/suspending potentially more at-risk DMTs in every single person with MS (Berger et al., 2020; Brownlee et al., 2020), also accounting for age and comorbidities (increasing the risk of morbidity and mortality from COVID-19) (Gabutti and Federica, 2020). In particular, though safer DMTs should be used whenever possible, we have added some suggestions, implying that SARS-CoV-2 will be part of our clinical practice in the upcoming months. In particular, for natalizumab and anti-CD20 antibodies, depending on regulatory indications, extended interval dosing could be considered, if necessary, to improve logistics of healthcare delivery, by reducing the number of people attending the infusion room and, more in general, the number of hospital accesses (Clerico et al., 2020). For dimethyl fumarate and teriflunomide, during follow-up, we suggest more frequent full blood cell count (FBC) if lymphocytes < 800/μL (e.g., forth monthly), whilst treatment should be stopped if lymphocytes < 500/μL (Wijnands et al., 2018). Similar recommendations apply to S1P inhibitors (e.g., fingolimod, siponimod), though alternate doses could be considered (e.g., if lymphocytes < 500/μL continuously) before treatment discontinuation (if lymphocytes < 200/μL) (Wijnands et al., 2018; Luna et al., 2020). For pulse treatments (alemtuzumab, anti-CD20 antibodies, autologous haematopoietic stem cell transplantation, cladribine), we suggest patients carefully self-isolate for 14 days before treatment (or re-treatment), corresponding to SARS-CoV-2 longest incubation period (Gabutti and Federica, 2020; Zappulo et al., 2019). Also, after treatment, patients treated with pulse treatments should wear protective surgical-grade masks, and should self-isolate or, at least, limit contacts with people, also accounting for individual changes in lymphocyte count. For pulse treatments and for S1P inhibitors, we suggest serological test for IgG and IgM anti-SARS-CoV-2, and/or oro-pharyngeal swab for SARS-CoV-2 RT-PCR. Ideally, serological test and oro-pharyngeal swab should be combined whenever possible, or, at least, in pulse treatments responsible for long-term and/or wide immunosuppression (e.g., alemtuzumab, autologous haematopoietic stem cell transplantation). Though the oro-pharyngeal swab for SARS-CoV-2 RT-PCR is the current gold standard for COVID-19 diagnosis (Gabutti and Federica, 2020), serological test for IgG and IgM anti-SARS-CoV-2 is expected to increase in sensibility and specificity in the upcoming months. We are currently using a test with 88.66% sensitivity and 90.63% specificity, which detects SARS-CoV-2 IgM and IgG in 15 min (Li et al., 2020), and, thus, can be performed immediately before commencing on treatment. Of course, in the presence of IgM or IgG, a diagnosis of active infection should be necessarily excluded with oro-pharyngeal swab for SARS-CoV-2 RT-PCR. This test has been validated by Li and colleagues (Li et al., 2020), and its use has been approved by local regulatory agencies.

While developing the SAFE pathway, we had to account for possible risks coming from SARS-CoV-2 asymptomatic carriers (Gandhi et al., 2020), and from limitations of current diagnostic tools (e.g., relatively high number of false negatives to COVID-19 testing) (Looefelho and Tang, 2020). Thus, to reduce the risk of infection in patients treated with potentially more at-risk DMTs we have adopted a combination of several containment measures (e.g., COVID-19 testing on asymptomatic patients, self-isolation before and after treatment, face masks) (Gandhi et al., 2020). In the future, national and international experiences on the effects of DMTs on COVID-19, along with the evolution of the pandemic, will possibly change our pathway, though it could be still helpful in the case of new COVID-19 outbreaks, and/or as a general preventative measure to COVID-19 (as already in place for other respiratory and non-respiratory infections, such as tuberculosis, varicella zoster, or hepatitis).

Our SAFE pathway is the result of local arrangements and its generalizability to other healthcare systems should be evaluated. Unfortunately, we have not been able to collect patient-reported outcome measures for patients’ satisfaction, though our protocol has been certainly made easier by local regulations (e.g., compulsory use of face masks at population level and strong enforcement of self-isolation policies). However, through the SAFE pathway, we have been able to commence on or re-dose pulse treatments in more than 50 patients,
from April to May 2020, without any recorded case of COVID-19. In these difficult times, our thoughts go to the front-line staff facing the COVID-19 emergency, but our efforts should go also to the most vulnerable patients with chronic diseases. Until a safe and effective vaccine is available at population level, in the upcoming months, we believe our COVID-19 SAFE pathway for MS management will be helpful to prevent irreversible disability accrual and long-term consequences, whilst maintaining MS patients safe.

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Declaration of Competing Interest

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References

Amor, S., Baker, D., Rhoury, S., Schmiereier, K., Giovannoni, G., 2020. SARS-CoV-2 and Multiple Sclerosis: Not All Immune Depleting DMTs are Equal or Bad. Ann. Neurol. https://doi.org/10.1002/ana.25779.

Baker, J.R., Brandstädter, R., Bar-or, A., 2020. COVID-19 and MS disease-modifying therapies. Neurology. Neuroimmunoinflammation e761. https://doi.org/10.1212/NXI.0000000000000761.

Brownlee, W., Bourdette, S., Bradby, S., Killestein, J., Ciccarelli, O., 2020. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. Neurology. https://doi.org/10.1212/WNL.0000000000009957.

Burdick, S., Montgomery, S., Hajiebrahimi, M.H., Hillert, J., Olsson, T., Bahmanyar, S., 2020a. Multiple sclerosis in the Campania Region (South Italy): algorithm validation and 2015–2017 prevalence. Int. J. Environ. Res. Public Health 17, E1388. https://doi.org/10.3390/ijerph1701388.

Clerico, M., De Mercanti, S., Signori, A., Iudicello, M., Cordioli, C., Signoriello, E., et al., 2020. Extending the Interval of Natalizumab Dosing: is Efficacy Preserved. Neurotherapeutics 17, 200–207. https://doi.org/10.1007/s13311-019-00776-7.

Cohen, J., 2020. Vaccine designers take first shots at COVID-19. Science 368, 14–16. https://doi.org/10.1126/science.368.6486.14.

Gabotti, G., Federica, A., 2020. Coronavirus: update Related to the Current Outbreak of COVID-19. Infect. Dis. Ther. https://doi.org/10.1007/s40121-020-00295-5.

Gandhi, M., Yokoe, D., Havlir, D., 2020. Asymptomatic Transmission, the Achilles’ Heel of Current Strategies to Control Covid-19. N. Engl. J. Med. 382, 2158–2160. https://doi.org/10.1056/NEJMe2009758.

Hughes, R., Pedotti, R., Koendgen, H., 2020. COVID-19 in persons with multiple sclerosis treated with ocrelizumab – a pharmacovigilance case series. Mult Scler Relat Disord. https://doi.org/10.1016/j.msard.2020.102185.

IHME COVID-19 health service utilization forecasting team, 2020. Forecasting COVID-19 impact on hospital bed-days, ICU-days, ventilator-days and deaths by US state in the next 4 months. Medrxiv. https://doi.org/10.1101/2020.03.27.20043752.

Leocani, L., Diserens, K., Moccià, M., Caltagirone, C., 2020. Disability through COVID-19 pandemic: neurorehabilitation cannot wait. Eur J Neurol. https://doi.org/10.1111/ene.14320.

Li, Z., Yi, Y., Luo, X., Xiong, N., Liu, Y., Li, S., et al., 2020. Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. J. Med. Virol. https://doi.org/10.1002/jmv.25727.

Loeffelholz, M.J., Tang, Y.W., 2020. Laboratory diagnosis of emerging human coronavirus infections-the state of the art. Emerg. Microbes Infect 9, 747–756. https://doi.org/10.1080/22221751.2020.1745095.

Luna, G., Alping, P., Burman, J., Fink, K., Fogdell-Hahn, A., Gunnarsson, M., et al., 2020. Infection Risks Among Patients with Multiple Sclerosis Treated with Fingolimod, Natalizumab, Rituximab, and Injectable Therapies. JAMA Neurol 77, 184–191. https://doi.org/10.1001/jamaneurol.2019.3365.

Moccia, M., Brescia Morra, V., Lanzillo, R., Loperto, I., Giordana, R., Fumo, M., et al., 2020. Extending the Interval of Natalizumab Dosing: is Efficacy Preserved. Neurotherapeutics 17, 200–207. https://doi.org/10.1007/s13311-019-00776-7.

Moccià, M., Brescia Morra, V., Lanzillo, R., Bonavita, S., Tedeschi, G., Leocani, L., et al., 2020. Assessing disability and relapses in multiple sclerosis on tele-neurology. Neurol Sci. https://doi.org/10.1007/s10072-020-04479-x.

Monteiro-escribano, P., Matias-guiu, J., Gómez-iglesias, P., Porta-ettesam, J., Pytel, V., Matias-guiu, J.A., 2020. Letter to the Editor. Mult. Scler. Relat. Disord 42, 102185. https://doi.org/10.1016/j.msard.2020.102185.

Sormani, M.P., and On behalf of the Italian Study Group on COVID-19 infection in multiple sclerosis, 2020. Correspondence an Italian programme for COVID-19 infection. Lancet Glob. Heal 4422, 3047. https://doi.org/10.1016/S1474-4422(20)30147-2.

Waldman, G., Mayeux, R., Claassen, J., Agarwal, S., Willey, J., Anderson, E., et al., 2020. Preparing a neurology department for SARS-CoV-2 (COVID-19): early experiences at Columbia University Irving Medical Center and the New York Presbyterian Hospital in New York City. Neurology. https://doi.org/10.1212/NW.0000000000009519.

Wijndans, J.M.A., Zhu, F., Kingswell, E., Fisk, J.D., Evans, C., Marrie, R.A., et al., 2018. Disease-modifying drugs for multiple sclerosis and infection risk: A cohort study. J. Neurol. Neurosurg. Psychiatry 89, 1050–1056. https://doi.org/10.1136/jnnp-2017-317493.

Zappulo, E., Buonomo, A.R., Saccà, F., Russo, C.V., Scotto, R., Scalia, G., et al., 2019. Incidence and Predictive Risk Factors of Infective Events in Patients With Multiple Sclerosis Treated With Agents Targeting CD20 and CD52 Surface Antigens. Open Forum Infect Dis 6, ofz445. https://doi.org/10.1093/ofid/ofz445.

Antonio Buonomo a, Vincenzo Brescia Morra a, Emanuelia Zappulob, Roberta Lanzillo b, Ivan Gentile a, Emma Montella b, Maria Triassib, Raffaele Palladino a, Marcello Moccia a

a Section of Infectious Diseases, Department of Clinical Medicine and Surgery, Federico II University of Naples, Italy

b Multiple Sclerosis Clinical Care and Research Centre, Department of Neuroscience, Reproductive Science and Odontostomatology, Federico II University of Naples, Italy

c UNESCO Chair on Health Education and Sustainable Development, Federico II University of Naples, Italy

d Department of Hygiene, Preventive and Industrial Medicine, Federico II University Hospital, Naples, Italy

e Department of Public Health, Federico II University of Naples, Italy

f Department of Primary Care and Public Health, Imperial College London, United Kingdom

⁎ Corresponding author at: Marcello Moccia: Multiple Sclerosis Clinical Care and Research Centre, Department of Neuroscience, Reproductive Science and Odontostomatology, Federico II University of Naples, Via Sergio Pansini 5, 80131 Naples, Italy.