Correspondence

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

A B S T R A C T

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-milion inhabitants. Thus, the curve of the epidemic has been reasonably flat, with less than 5000 cumulative cases in the following two months (by comparison, in a same-sized population, Denmark recorded more than 10,000 cumulative cases) (IHME COVID-19 health service utilization forecasting team, 2020), and the healthcare system has not been overwhelmed by the emergency. In this reasonably-calm scenario, over the past months, MS, infective disease, and public health specialists from the largest centre of the region (Federico II University of Naples,

Italy) (Moccia et al., 2020a), have developed (and applied) a protocol for delivering the same quality of services to people with MS, while 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:

- **S**CREEN. 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.
- **A**CCESS. 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.
- **F**ACE. 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

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 - 14-day self-isolation	- Protective surgical-grade masks - Self-isolation or reduction in social contacts (also accounting for lymphocyte count)
Anti-CD20 *(ocrelizumab, rituximab)*	- SARS-CoV-2 serological testing and/ or oro-pharyngeal swab - 14-day self-isolation	- Protective surgical-grade masks - Self-isolation or reduction in social contacts (also accounting for lymphocyte count) - Extended interval dosing, following CD19 lymphocyte count and in accordance with regulatory indications (if needed for social distancing in the infusion room)
Autologous haematopoietic stem cell transplantation	- SARS-CoV-2 serological testing and/ or oro-pharyngeal swab - 14-day self-isolation	- Protective surgical-grade masks - Self-isolation or reduction in social contacts (also accounting for lymphocyte count)
Cladribine	- SARS-CoV-2 serological testing and/ or oro-pharyngeal swab - 14-day self-isolation	- Protective surgical-grade masks - Self-isolation or reduction in social contacts (also accounting for lymphocyte count)
Dimethyl fumarate	- As usual	- More frequent FBC if lymphocytes $<800/\mu L$ - Stop if lymphocytes $<500/\mu L$
Glatiramer acetate	- As usual	As usual
Interferon-beta	- As usual	- As usual
Natalizumab	- As usual	- Extended interval dosing, in accordance with regulatory indications (if needed for social distancing in the infusion room)
S1P inhibitors *(fingolimod, siponimod)*	- SARS-CoV-2 serological testing and/ or oro-pharyngeal swab	- More frequent FBC if lymphocytes $<500/\mu L$ - Alternate doses if lymphocytes $<500/\mu L$ continuously - Stop if lymphocytes $<200/\mu L$
Teriflunomide	- As usual	- More frequent FBC if lymphocytes $<800/\mu L$ - Stop if lymphocytes $<500/\mu L$

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 on-line 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 $<800/\mu L$ (e.g., forth monthly), whilst treatment should be stopped if lymphocytes $<500/\mu L$ (Wijnands et al., 2018). Similar recommendations apply to S1P inhibitors (e.g., fingolimod, siponimod), though alternate doses could be considered (e.g., if lymphocytes $<500/\mu L$ continuously) before treatment discontinuation (if lymphocytes $<200/\mu L$) (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 have 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) (Loeffelholz 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.

Disclosures

Authors have nothing to disclose.

Declaration of Competing Interest

Authors have nothing to disclose.

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