Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Establishment of a safety protocol for the administration of treatments in multiple sclerosis during the SARS-CoV-2 pandemic

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The new coronavirus SARS-CoV-2 detected in December 2019 in Wuhan, China, caused the epidemic disease known as coronavirus disease 2019 (COVID-19). This pandemic, affecting thousands of people worldwide and spreading rapidly, has become a global threat (Lai C-C et al). The pandemic has presented Multiple Sclerosis (MS) neurologists with new uncertainties and a changing reality, forcing us to make decisions quickly with a lack of available evidence. It is currently unclear whether MS patients are exposed to a greater risk of severity upon SARS-CoV-2 infection (Brownlee et al., 2020, Maria Pia, 2020), although the use of some disease-modifying drugs may entail an additional infection risk for these patients (Wijnands et al., 2018) and many of these drugs are also contraindicated in cases of active infection.

In order to minimize the risk associated with administering immunosuppressive treatments, it has been proposed to postpone as long as possible the use of those with a higher risk of inducing lymphopenia in the short to medium term and to use extended administration for other drugs (Brownlee et al., 2020, Costa-Frossard et al., 2020). In patients treated with these drugs or patients with a possible MS relapse, SARS Cov2 infection should also be carefully ruled out as a cause of clinical deterioration and the use of steroids should be considered only in those patients with relapses leading to increased disability (Brownlee et al., 2020, Costa-Frossard et al., 2020)

There are a number of reasons why protocols are needed for safe administration of MS treatments:

2- The COVID-19 incubation period is variable, ranging from 0 to 24 days (Huang et al., 2020)
2- Asymptomatic carriers can spread the virus. Immunosuppressive treatments, by modifying the immune response, could activate asymptomatic infections or those in the incubation period. Although such cases are yet to be described, we must take this theoretical concept into account (Yan Bai et al., 2020, Ye et al., 2020 May)
2- Clinical reactivation of infection, i.e. the reappearance of a new infectious case, has been described (Ye et al., 2020 May). These patients presented negative PCR following the first clinical picture, with a reactivation window period from negative to positive SARS-CoV-2 and a new clinical picture within 4 to17 days. Corticosteroids were used in most of this reactivated patients. This suggests that recovered patients may still carry the virus, which could be re-activated by certain conditions, such as immunosuppression (Ye et al., 2020 May). The existence of false negatives could lead to these presumed 'reactivations' being interpreted erroneously. Perhaps these patients are still convalescing from their first clinical symptoms (Xiao et al., 2020). In any case, the detection of such cases is important. We have had a similar experience with clinical reactivation of a patient after taking a dose of immunosuppressant. This is one of the things that led us to conduct the current work.

Despite all this, we must bear in mind that it is unproven (Maria Pia, 2020) whether patients receiving immunosuppression are at greater risk in this pandemic because of the differential characteristics of COVID-19. It is thought that this disease develops in different phases, with the most severe caused by cytokine release syndrome and hyper-inflammatory state, as well as changes resulting from vascular pathology and thrombosis (Wichmann et al., 2020). In reference to hyper-inflammation, it has been postulated that the previous use of selective immunosuppressive drugs could even offer a protective mechanism (Costa-Frossard et al., 2020, Huang et al., 2020, Siddiqu, and Mehra). Until the evidence increases, however, and in our experience of patient management, our action protocol must focus on safety.

The most commonly used technique for diagnosing SARS-CoV-2 infection is to detect viral RNA using RT-PCR in nasopharyngeal swabs (Yan Bai et al., 2020). The positive results of this technique depend on the presence of sufficient quantity of viral genome at the sample extraction site, as well as on the sample collection technique, which can lead to false negatives (Guo et al., 2020). Negative results may also be obtained when the virus cannot be detected in the exudate because the patient is at an early stage of the disease (window period), the host's immunity has suppressed it, or if samples are obtained late in the course of infection (Zhao et al., 2020).

Blood testing for IgM against the virus, a marker of acute infection, can increase diagnostic sensitivity from 51.9% to 98.6%. It also seems that IgM can remain detectable for longer than viral RNA (Guo et al., 2020). IgM testing may, however, give false negatives if the samples are taken at the beginning of infection, since IgM has been observed from the fifth day of infection (Guo et al., 2020). IgG, on the other hand, a

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Table 1
Early days of the pandemic. The protocol includes an epidemiological survey (questionnaire shown in Annex 1). If questionnaire was positive, a PCR was performed on nasopharyngeal swabs.

EPIDEMIOLOGY CONTACT	PCR	INTERPRETATION	ACTION
-	N/A	NO SARS-CoV-2 CONTACT	ADMINISTER TREATMENT
+	+	ACTIVE INFECTION (WINDOW PERIOD) VS ASYMPTOMATIC CARRIER	- POSTPONE TREATMENT REPEAT PCR 7 DAYS LATER
+	-	NO SARS-CoV-2 CONTACT VS PAST INFECTION (ASYMPTOMATIC) VS WINDOW PERIOD	- POSTPONE TREATMENT - REPEAT PCR 7 DAYS LATER

N/A: NOT APPLICABLE

Table 2
Pandemic established. The protocol includes IgG + IgM serology. This technique helps us to increase our diagnostic capacity but does not provide information on patients' degree of immunization. Two negative PCRs are necessary for administering treatment. PCR re-test is performed 7 days later.

1st PCR	IgG + IgM	2nd PCR	INTERPRETATION	ACTION
-	-	N/A	NO SARS-CoV-2 CONTACT	ADMINISTER TREATMENT
-	+	-	PAST AND RECOVERED INFECTION VS PAST ASYMPTOMATIC CARRIER	ADMINISTER TREATMENT
-	+	+	ACTIVE INFECTION (WINDOW PERIOD) VS RECOVERED INFECTION VS ASYMPTOMATIC CARRIER (FALSE NEGATIVE PCR)	- POSTPONE TREATMENT - REPEAT PCR 7 DAYS LATER
+	+	+	ACTIVE INFECTION (WINDOW PERIOD) VS RECOVERED INFECTION VS ASYMPTOMATIC CARRIER	- POSTPONE TREATMENT - REPEAT PCR 7 DAYS LATER
+	+	-	PAST INFECTION VS ASYMPTOMATIC CARRIER	- POSTPONE TREATMENT - REPEAT PCR 7 DAYS LATER
+	-	+	ACTIVE INFECTION (WINDOW PERIOD) VS ASYMPTOMATIC CARRIER NOT IMMUNIZED	- POSTPONE TREATMENT - REPEAT BOTH TESTS 7 DAYS LATER
+	-	-	ACTIVE INFECTION (WINDOW PERIOD) VS ASYMPTOMATIC CARRIER NOT IMMUNIZED	- POSTPONE TREATMENT - REPEAT BOTH TESTS 7 DAYS LATER

N/A: NOT APPLICABLE

Table 3
Quarantine de-escalation measures will gradually be implemented with a high percentage of infected and recovered patients.

PCR	IgG	IgM	INTERPRETATION	ACTION
-	-	-	NO SARS-CoV-2 CONTACT	ADMINISTER TREATMENT
-	+	-	PAST AND RECOVERED INFECTION	ADMINISTER TREATMENT
-	-	+	ACTIVE INFECTION (WINDOW PERIOD) VS ASYMPTOMATIC CARRIER (FALSE NEGATIVE PCR)	- POSTPONE TREATMENT - REPEAT BOTH TESTS 7 DAYS LATER
-	+	+	ACTIVE INFECTION (WINDOW PERIOD) VS ASYMPTOMATIC CARRIER (FALSE NEGATIVE PCR)	- POSTPONE TREATMENT - REPEAT BOTH TESTS 7 DAYS LATER
+	+	+	ACTIVE INFECTION (WINDOW PERIOD) VS ASYMPTOMATIC CARRIER	- POSTPONE TREATMENT - REPEAT BOTH TESTS 7 DAYS LATER
+	+	-	PAST AND RECOVERED INFECTION	- POSTPONE TREATMENT - REPEAT PCR 7 DAYS LATER
+	-	+	ACTIVE INFECTION (WINDOW PERIOD) VS ASYMPTOMATIC CARRIER	- POSTPONE TREATMENT - REPEAT BOTH TESTS 7 DAYS LATER
+	-	-	ACTIVE INFECTION (WINDOW PERIOD) VS ASYMPTOMATIC CARRIER (NOT IMMUNIZED VS FALSE NEGATIVE)	- POSTPONE TREATMENT REPEAT BOTH TESTS 7 DAYS LATER

ADMINISTER TREATMENT
CONFIRM WITH PCR
CONFIRM WITH PCR + SEROLOGY

marker of late immunity, appears around day 14 (Guo et al., 2020, Zhao et al., 2020), with levels increasing until around day 21, when a sustained 'plateau' can be reached (Guo et al., 2020). ELISA IgM and IgG testing has greater than 95% specificity and the use of this technique together with PCR at the onset and in the following two weeks can further increase diagnostic accuracy (Sethuraman et al., 2020). This increased diagnostic sensitivity using both PCR and serology has been confirmed in various recent works (Soelberg Sorensen, 2017), reaching sensitivity and specificity levels of up to 100% (Long et al., 2020). In general, most antibodies are produced to combat the most abundant viral protein, NC, and these tests are therefore the most sensitive (Sethuraman et al., 2020). There are several rapid tests of varying quality available on the market that do not in some cases detect precisely the antigens used (Sethuraman et al., 2020).

We present the safety protocol for treating MS patients established in our MS Unit and its development over the pandemic period. Our aim is not to establish the sensitivity and specificity of the tests used; these findings could be presented in a subsequent broader. Our aim, instead, is to present the safety protocol used in MS patients.

We have used a dynamic protocol adapted to the development of the pandemic. During the early days of the pandemic, the first measure was to postpone doses of certain immunosuppressive treatments due to rapid spread of the virus and saturation of emergency services. The need to avoid MS reactivation in our patients, however, led us to implement several protocols for administering treatments as safely as possible.

The protocol applies to administering initial doses and all re-doses of natalizumab, ocrelizumab, rituximab, cladribine and alemtuzumab, as well as initial doses of teriflunomide, dimethyl fumarate, fingolimod, and methyl prednisolone in relapses. Injectables are excluded because

of their reduced impact on the immune system (Soelberg Sorensen, 2017). We stop the protocol in patients where recovery from COVID-19 has been demonstrated.

1st action. Online/telephone pre-treatment interview (2-7 days before treatment):

a) Symptomatic: treatment suspension and subsequent general medicine assessment
b) Asymptomatic: PCR testing and SARS-CoV-2 serology

2nd action. PCR testing and serology: 1-7 days before treatment (Sethuraman et al., 2020)

Test interpretation and actions taken are detailed in Tables 1-3. Each table corresponds to different moments during the pandemic and different levels of resource availability. Where necessary, results are confirmed at 7 days. It is possible for PCR to remain positive for more than 7 days (Guo et al., 2020), but testing is done at 7 days with the aim of conducting close monitoring and not unduly postponing treatment. It is combined with antibodies to increase case detection rates (Guo et al., 2020, Long et al., 2020, Xiang et al., 2020).

If a patient presents COVID-19, the protocol is applied at least 15 days after the complete disappearance of symptoms. If a patient has suspended MS treatment during COVID-19, treatment can only be restarted when COVID-19 is not active according to the protocol and there is no risk of disease relapse associated with each drug (Brownlee et al., 2020, Costa-Frossard et al., 2020).

Finally, it is crucial to individualize treatment in each patient. Treatment decisions (maintaining, suspending or delaying treatment) must be individualized and take into account associated risk factors (age, comorbidities, etc.) (Brownlee et al., 2020, Costa-Frossard et al., 2020).

1. CONCLUSIONS

We consider that the ideal scenario would be to perform PCR together with IgG and IgM serology testing in all patients scheduled to receive immunosuppressive treatment. We do not currently have a way of interpreting serology tests with absolute certainty. Nevertheless, in addition to increasing diagnostic sensitivity in negative cases (Guo et al., 2020, Long et al., 2020, Xiang et al., 2020), this could increase the safety with which treatments are initiated by reducing the possibility of reactivating the virus after treatment.

Our protocol offers safety to our MS patients. The simplicity and versatility of our protocol allows it to be applied in different regions with differing pandemic statuses.

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