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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Correspondence

Treating patients with multiple sclerosis during the COVID-19 pandemic: Assessing the expert recommendations

Dear Sir

Currently, it is estimated that the SARS-CoV-2 virus has infected almost four million people around the world and caused nearly three hundred thousand casualties (European Centre for Disease Prevention and Control, (ECDPC), 2020), with respiratory failure being the main cause of death (Ruan et al., 2020). By the end of February 2020 the first cases were reported in Latin-America (Rodriguez-Morales et al., 2020). In Chile the first case was confirmed on the March 3rd and on the 18th of March authorities declared a state of emergency with 238 confirmed cases of COVID-19 (Ministry of Health of Chile). Since then the disease has had a consistent increase with a total of 41 428 confirmed cases up to May 16th, which can be translated to 2 212 confirmed cases per million people (ECDPC, 2020). Patients with multiple sclerosis (pwMS) using disease-modifying treatments (DMT) can present a varying degree of immunodeficiency that can translate into an increased risk of infections and of infections causing hospitalization (Luna et al., 2019; Persson et al., 2020). Whether pwMS are at increased risk of COVID-19 or at higher risk of developing more severe complications is unknown (Brownlee et al., 2020). As of April 7th 2020, 57 pwMS have tested positive for COVID-19 in Italy and, of six patients in critical conditions, one recovered and five died (Sormani, 2020). In this context of absence of clear evidence-based guidelines, expert recommendations on the management of pwMS during the COVID-19 pandemic have rapidly emerged, with the Italian Society of Neurology (ISN) and the Association of British Neurologists (ABN) releasing the first examples. Overall, both groups consider safe to start or continue treatment with first line (interferons β, glatiramer acetate, teriflunomide, dimethyl fumarate) and non-lymphodepleting second line DMTs such as fingolimod and natalizumab. In relation with lymphodepleting DMTs (alemtuzumab, ocrelizumab, rituximab or cladribine), the recommendations are less straightforward, focusing on individual factors such as disease activity and lymphocyte count, but generally suggesting to temporarily delay the start or dosing (between 6 to 12 months). Nevertheless, other experts have expressed concern that such recommendations may be inadequate in pwMS with a highly active form of MS, in agreement with the saying *Time is brain*. In all cases any increased risk of infection and associated morbidity will need to be carefully balanced against the risks of stopping treatment and facing a rebound of disease activity (Giovannoni et al., 2020; Willis and Robertson, 2020).

Quarantine is the restriction of persons who are presumed to have been exposed to a contagious disease but who are not ill. It may be applied at an individual, group, or community level and involves restriction of staying at home or in a designated facility (Cetron and Landwirth, 2005). Quarantine can be implemented on a voluntary basis or can be legally enforced by authorities (Nussbaumer-Streit et al., 2020). At first, the Chilean national health authorities have avoided a mandatory quarantine. However, the ABN and ISN recommendations gave us a framework for the decision-making process and our pwMS were asked to follow a voluntary quarantine by telephone and advised to continue, delay or interrupt DMT schedules according to individualized assessments.

We aim to report the decision-making process inspired by the ISN and ABN recommendations under the threat of the COVID-19 pandemic from the end of February until 30th April 2020. Fifty-two adult pwMS on DMTs were followed at the University of Chile Hospital, in Santiago, Chile, including 18 patients that required in-hospital infusions. On April 30th all of them were interviewed by telephone on whether they had followed Word Health Organization (WHO) on preventive measures to reduce transmission of COVID-19. According to the recommendations made by the ISN guideline, they were also asked whether they were following a voluntary quarantine. Additional questions centred on whether they had acquired COVID-19 infection or had been close to a person with SARS-CoV-2 infection. For patients with alemtuzumab, natalizumab and ocrelizumab, absolute lymphocyte counts are reported. Prior to inclusion, patients provided informed written consent for participation in the study FONIS SA1610026. The project was approved by the local research ethics committees of the University of Chile Hospital, Santiago, Chile.

The mean age of the patients is 34 years (SD ± 11), 69% are women, with mean disease duration of 3 years (SD ± 2) and mean Expanded Disability Status Scale (EDSS) score of 1.6 (SD ± 1.7). Ninety percent of the patients have relapsing remitting multiple sclerosis (RRMS) and 10% primary progressive multiple sclerosis (PPMS). The DMTs are shown in Table 1. All 52 pwMS have followed WHO guidance to reduce transmission of COVID-19. Eighty-five percent have followed a voluntary quarantine. None of them have been diagnosed with COVID-19 (Table 2). Patients on interferons, glatiramer acetate and fingolimod have continued their treatments without changes. Infusions of natalizumab have continued without changes; treatments with ocrelizumab have been started in three patients with severe and active disease and re-dosings have been postponed in three patients. There have not been issues with absolute lymphocyte counts (ALC) in patients with either natalizumab or ocrelizumab. The last infusions of alemtuzumab took place at the end of February when two patients with severe disease received their second cycle. The first was a 25-year-old female with an initial ALC of 1288/mm^3 who presented an ALC one month after the infusion of 22/mm^3, and 247/mm^3 two months later. The second patient was a 26-year-old male whose ALC count fell ten days post-infusion from 1500/mm^3 to 136/mm^3 and increased to 364/mm^3 after a month and a half (Table 1).

In the acute phase of the COVID-19 pandemic, pwMS in Santiago of Chile are very aware of the putative risks associated to their immunological status and have taken additional protective measures. No one had developed COVID-19 disease after two months since Chile entered a state of emergency. As seen in Table 1, patients treated with alemtuzumab are facing this pandemic with a low lymphocyte count

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Table 1
Patients characteristics, disease modifying treatment and lymphocyte count

Characteristics	n = 52	
Age (mean ± SD)	34.1 ± 11.4	
Female, n (%)	36 (69.2)	
Disease type, n (%); EDSS (mean ± SD)		
RRMS	47 (90.4); 1.2 ± 1.4	
PPMS	5 (9.6); 5.4 ± 1.3	
Treatment, n (%)		absolute lymphocyte count, mean and range
Interferon	11 (21.2)	
Glatiramer acetate	4 (7.7)	
Fingolimod	19 (36.5)	
Natalizumab	3 (5.8)	3674 (2834 -4514)
Ocrelizumab	6 (11.5)	3000 (1700-4300)
Alemtuzumab	9 (17.3)	690 (22 – 1630)
Comorbidities, n (%)		
None	38 (73%)	
Glucose intolerance	2 (3.8%)	
High blood pressure	2 (3.8%)	
Depression	4 (7.7%)	
Diabetes mellitus	1 (1.9%)	
Carcinoma of the uterine cervix	1 (1.9%)	
Smoking	1 (1.9%)	
Hypothyroidism	1 (1.9%)	
Ehlers-Danlos Syndrome	1 (1.9%)	
Psychosis-like	1 (1.9%)	

RRMS: Relapsing remitting multiple sclerosis; PPMS: Primary progressive multiple sclerosis

Table 2
Questionnaire's results

Question	Relative frequency (percentage)
Confirmed COVID-19	0/52 (0%)
Confirmed case contact	1/52 (1.9%)
COVID-19 symptoms	1/52 (1.9%)
Following general recommendations	52/52 (100%)
Preventive quarantine	45/52 (86.5%)
Anxiety level	
None	36/52 (69.2%)
Mild	6/52 (11.5%)
Moderate	9/52 (17.3%)
Severe	1/52 (1.9%)
Disease status perception	
Controlled	45/52 (86.5%)
Non-controlled	7/52 (13.5%)

($< 800/mm^3$).

There are many challenges when conducting research during a pandemic. Rapid investigations are usually narrow in scope and unable to answer broader questions about the illness (Fowler et al., 2010). The results of this study should be interpreted in the light of the small sample size and considering that coronavirus cases are increasing rapidly in this country as in the rest of Latin-America. We will continue to monitor these patients throughout the duration of the pandemic.

There is broad agreement that first-generation DMTs do not increase the risk of infection and could be even beneficial in the case of interferon β because of its antiviral characteristics, but second-generation DMTs have shown to augment patient's risk of developing viral diseases (Luna et al., 2019; Wijnands et al., 2018). As trials for the generation of solid evidence are on course and vaccines take time to be developed, uncertainty rises, especially in pwMS receiving DMT with an immunosuppressive role. It has also been suggested that a group of patients with COVID-19 may have a cytokine storm syndrome in which immunosuppression may be beneficial (Mehta et al., 2020; Novi et al., 2020), although other authors have mentioned the possible risks of treating patients with immunosuppressors stating that this association established between disease severity and presence of inflammatory cytokines may not necessarily be one of causality (Ritchie and Singanayagam, 2020; Russell et al., 2020).

The rationale and reasons for developing rapid guidelines are mainly related to health emergencies, rapid increases in cases of a particular condition, unusually severe disease, or the emergence of new evidence in relation to treatment modalities (Pang and Amul, 2018). The day Chile entered a state of emergency due to the COVID-19 pandemic Chilean neurologists had different views on how to treat pwMS and diverse local recommendations were followed. However, the ISN and ABN recommendations quickly appeared and were found to be very useful for local MS-specialists and rapidly were translated into Spanish. These guidelines helped us to indicate appropriate general safety measures for our patients and visualize any reasonable differences between DMTs potential risks of causing severe complications associated with the COVID-19 disease. The decision to start, continue or stop treatment with a given DMT should be strongly influenced by whether pwMS do or do not follow recommendations to prevent exposure to the virus. In addition, the exclusion of alemtuzumab in pandemic times seems to be a sensible measure because of the strong acute post-infusion lymphodepletion.

Declaration of Competing Interests

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