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LETTER TO THE EDITORS

COVID-19 in dimethyl fumarate-treated patients with multiple sclerosis

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Dear Editor,

Despite a few initial reports [1–5], the risk and course of COVID-19 in patients with multiple sclerosis (MS) is still unclear. Although neurological disability and comorbid conditions may be important factors, the role played by immune-based disease-modifying therapies (DMTs) in patients with MS has attracted the most attention in this regard [6]. Patients with MS have a generally increased risk of infections [7], particularly those with more severe disability or significant co-morbidities, with evidence for a role for infections in triggering MS relapses or worsening pre-existing MS symptoms [8]. MS patients are generally twice as likely to be hospitalized for infections than the general population [9].

Recently, Maghzi et al. [10] reported in this journal a case series of five teriflunomide-treated MS patients who developed COVID-19 infection and continued their therapy with a self-limiting infection and without any relapse. The authors hypothesized that the immune-biologic mechanisms pertaining to teriflunomide have a potential role in favoring a COVID-19-positive outcome.

Here, we would like to draw attention to another oral DMT. We report a case series of seven patients treated with dimethyl fumarate (DMF) that developed a self-limiting COVID-19 infection, during the peak of COVID cases in Lecco's province between March and May 2020. The diagnosis was based on the typical symptoms of COVID-19 infection (dry cough, anosmia, ageusia, fever, asthenia, and shortness of breath, see Table 1), associated with contacts with COVID-19-confirmed or suspected (respectively in 5 and 1 cases) subjects. Nasal swab and chest X-ray/CT were not performed due to the local guidelines at the time. All patients continued their therapy with DMF, and none of them experienced an MS relapse. Clinical characteristics and hematological values are reported in Table 1. Patients were mostly female (71%), with an average age of 35.9 (± 11.4) years and a disease duration of 6.71 (± 5.6) years. Median EDSS was 1.5 (range 1.5–2), and the average time on treatment with DMF was 2.4 (± 1.9) years. None had severe lymphopenia, and only one patient had grade two lymphopenia ($0.67 \times 10^3/\mu L$). No patient required hospitalization, ICU care, or intubation. They all improved without receiving any specific treatment. One of the patients reported left hand paresthesia during the respiratory symptoms, interpreted as a pseudo-relapse by the treating neurologist.

To date, there are no reported cases of COVID-19 infections in DMF-treated patients. The mechanism of action of DMF has still not been fully elucidated, and may be mediated both by nuclear factor (erythroid-derived 2)-like 2 (Nrf2)-dependent and independent pathways [11, 12]. DMF mechanism of action includes promotion of Th1–Th2 shift, induction of mild apoptosis of memory T cells and B cells, modulation of microglia activation, and neuroprotective effect by upregulation of Nrf2-dependent antioxidant response [13–16]. These immunomodulatory effects may be protective against the cytokine storm [17] in patients infected with SARS-COV-2, which has been postulated as one of the mechanisms underlying a more severe disease.

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Table 1 Summary of cases

Patient	Age	Sex	MS type	MS duration (years)	EDSS	Years on DMF	ALC (K/uL)*	CBC/LFTs*	Co-morbidities	Contact with COVID	Symptoms and duration
1	32	F	RR	3	1.5	1.5	1.24	WNL	No	Yes	Fever, dry cough for 7 days, pseudo-relapse of MS symptoms
2	50	M	RR	13	1.5	5	0.92	WNL	No	Yes	Fever, anosmia, shortness of breath for 5 days
3	36	F	RR	9	1.5	3	1.30	WNL	No	Suspected	Fever, dyspnea, dry cough for 7 days
4	23	M	RR	0.5	2	0.5	1.95	WNL	No	Yes	Anosmia and ageusia for 10 days
5	36	F	RR	7	2	1.5	1.33	WNL	No	Yes	Fever, dry cough, anosmia for 7 days
6	23	F	RR	0.5	2	0.5	1.83	WNL	No	No	Fever, headache, asthenia, anosmia for ten days
7	51	F	RR	14	1.5	5	0.67	WNL	No	Yes	Fever, dry cough, asthenia, anosmia for 10 days

ALC absolute lymphocyte count, *CBC* complete blood count, *EDSS* Expanded Disability Status Scale score, *LFTs* liver function tests, *MS* multiple sclerosis, *RR* relapsing–remitting, *WNL* within normal limits

*At nearest available time preceding COVID-19 infection

On the other hand, DMF, by reducing the lymphocyte count in a subset of patient may theoretically increase their risk of COVID-19. In a post-marketing prospective study, 4–6% out of 886 MS patients exposed to DMT developed grade III lymphopenia [18]. Nonetheless, serious infections are rarely reported in DMF-treated patients and occurred in ≤5% of patients, with no association between lymphopenia and increased incidence of infection [19].

This study has several limitations. The diagnosis of COVID-19 was based on clinical symptoms. The small number of patients, their young age, and low EDSS; and the presence of only a single case with moderate lymphopenia limit the generalizability of these observations.

As it has been reported for other MS DMTs, our case series suggest that continuing treatment with DMF might be safe in young and non-lymphopenic MS patients who develop COVID-19 infection, and its interruption does not seem to be necessary. Brownlee et al. [20] suggest that during the COVID-19 pandemic, it is perhaps safe to start DMF in children and young adults who are otherwise healthy. In patients already on treatment, they suggest continuing treatment and ensure that lymphocyte count is higher than 500-800/mm^3. These data give an insight into the management of MS patients during the COVID-19 pandemic, but further studies are necessary to confirm this preliminary observation, particularly in older, more disabled patients with significant co-morbidities.

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Compliance with ethical standards

Conflicts of interest VM, LA, and RB served in advisory boards and/or received travel grant from Biogen for participation at congress. PB, AS, BN, and CC have no conflict of interest to disclose.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All patients provided consent to be anonymously included in this report.

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