



COVID-19 in multiple sclerosis patients treated with dimethyl fumarate

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Dear Sirs,

We have read with great interest the paper published in this journal by Mantero et al. [1] reporting a case series of seven patients affected by multiple sclerosis (MS), in treatment with dimethyl fumarate (DMF), that developed a self-limiting SARS-CoV-2 infection and continued their therapy. To date, no other cases of COVID-19 in DMF-treated patients have been reported.

Here, we describe a further case-series of six patients, treated with DMF, that developed a mild form of COVID-19. Clinical features and hematological values are reported in Table 1.

Patients were all female, with an average age of 34.7 (± 13.2) years and a disease duration of 4.9 (± 3.1) years. Median EDSS was 2 (range 1–2.5). The average time on DMF treatment was 3.1 (± 1.9) years. Two patients presented comorbidities: hypertension treated with amlodipine 5 mg/die and ramipril 5 mg/die (patient #2), and the previous thyroidectomy for thyroid cancer, in replacement therapy with levothyroxine 137 μ g/die (patient #3). None had lymphopenia, neutropenia or leukopenia.

Regarding COVID-19, the diagnosis was based on a nasopharyngeal swab in all patients.

Different symptoms were reported by patients including gastrointestinal disturbances, fever, headache, fatigue, and loss of smell. The average duration of symptoms was 9.8 (± 5.9) days. Pharmacological treatments for COVID-19 were performed in 2 patients, including antibiotics (2/2),

corticosteroids (1/2), and paracetamol (2/2). No patient required hospitalization, ICU care, or oxygen support.

DMF was continued during the entire course of SARS-CoV-2 infection in all patients at the usual dosage (240 mg bid).

Compared with the patients presented by Mantero [1], in our cohort average time on treatment with DMF was about 0.7 years longer, disease duration 1.8 years shorter, and two patients had significant comorbidities. Age, gender, and median EDSS were quite similar between the two groups. Notably, in our cohort, SARS-CoV-2 infection was confirmed by nasopharyngeal swab in all patients.

Nowadays, there is wide discussion about the opportunity of continuing/stopping disease-modifying therapies (DMTs) in MS patients with COVID-19. The specific mechanisms of action of the various DMTs and patients' characteristics should be taken into account to individually stratify the COVID-19 risk in MS patients [2].

Theoretically, DMF could increase the COVID-19 risk because of its pleiotropic effects on the immune system including suppression of T and B cells [3, 4] and the potential induction of significant lymphopenia in a small percentage of patients [5]. On the other side, as postulated for other DMTs [6, 7], DMF could have a protective effect by modulating the immune response to SARS-CoV-2, one of the factors associated with the clinical severity of COVID-19.

Recently, Olgagnier et al. [8] demonstrated that the activation of the nuclear factor erythroid-derived 2-like 2 (NRF2) pathway by agonists such as DMF induces an antiviral program, distinct from the interferon pathway, that is effective in limiting virus replication and in suppressing the inflammatory responses induced by SARS-CoV2.

These experimental data suggest that DMF, not only does not increase the COVID-19 risks but it could also have a protective role against SARS-CoV-2. In this perspective, the benign course of COVID-19 observed in our case-series and in the patients described by Mantero [1] could be due, at least in part, to DMF therapy. However, the positive outcome

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Table 1 Clinical characteristics and hematological values of cases

Patient ID	Age	Gender	EDSS	MS type	Disease duration (years)	Years on DMF	DMF discontinuation during Covid-19 infection	Covid-19 symptoms	Covid-19 diagnosis	Comorbidities	Covid-19 therapy	Hospitalization	Oxygen support	ICU care	Covid-19 symptoms duration (days)
#1	26	F	1	RR	4	3.8	No	Nausea, diarrhea, fatigue, headache	Nasopharyngeal swab	No	Antibiotics, paracetamol	No	No	No	7
#2	58	F	2	RR	3	3	No	Fever, fatigue, loss of smell	Nasopharyngeal swab	Hypertension	Antibiotics, corticosteroids, paracetamol	No	No	No	10
#3	42	F	1	RIS	10	0.9 ^a	No	Fever, nausea and vomiting, diarrhea	Nasopharyngeal swab	Thyroidectomy in 2015 for thyroid cancer	None	No	No	No	2
#4	31	F	2	RR	6	5	No	Headache	Nasopharyngeal swab	No	None	No	No	No	10
#5	28	F	2.5	RR	1	0.6	No	Fatigue	Nasopharyngeal swab	No	None	No	No	No	20
#6	23	F	2	RR	5.5	5	No	Fever, loss of smell	Nasopharyngeal swab	No	None	No	No	No	10

EDSS Expanded Disability Status Scale, MS multiple sclerosis, DMF dimethyl fumarate, ICU intensive care unit

^aPatient #3 had taken DMF for 6 months in 2019, then she discontinued treatment for personal choice in June 2019 and finally, she restarted DMF in June 2020

might be unrelated to DMF, given that most patients recover spontaneously from COVID-19.

In conclusion, our small case-series confirms that continuing DMF might be safe in MS patients who have normal lymphocyte count and develop mild SARS-CoV-2 infection.

Available data are insufficient to draw definitive conclusions on the opportunity of continuing DMF in aged patients with significant comorbidities, lymphopenia, or severe forms of COVID-19 requiring hospitalization.

Additional studies are necessary to establish the most correct management of DMF therapy in these situations and to assess if this drug can have a protective role against SARS-CoV-2 as suggested by experimental findings.

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Availability of data and material (data transparency) Anonymized data will be shared with qualified external researchers, after approval of their requests.

Compliance with ethical standards

Conflicts of interest FC has received travel grants from Biogen, Merck, Sanofi-Genzyme, and Roche. EF has received travel grants from Biogen, Merck, Novartis, Sanofi-Genzyme, and Roche. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics 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.

Consent for publication All patients provided consent to be anonymously included in this report.

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