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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Asymptomatic SARS-CoV-2 infection in two patients with multiple sclerosis treated with fingolimod

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1. Summary

Fingolimod is a sphingosine 1 phosphate (S1P) receptor modulator, largely used in Multiple sclerosis (MS) treatment to reduce clinical and radiological disease activity. Fingolimod, binding to S1P receptors on lymphocytes, leads to receptor internalization and sequesters lymphocytes in lymph nodes, preventing them from contributing to the autoimmune reaction. Under fingolimod treatment lymphopenia is typically observed, and there is a small increase in the risk of herpes virus and respiratory tract infections (Arvin et al., 2015).

The novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pertains to the large family of Coronaviridae, which includes also MERS-CoV,SARS-CoV, and it causes a respiratory disease called COVID-19 (COronaVIrus Disease 19). Generally, COVID-19 is less severe than SARS, in fact, it can be a self-limiting disease in about 80% of patients, whilst serious bilateral interstitial pneumonia and multi organ failure may complicate the remaining 20% (Onder et al., 2020).

The first COVID-19 Italian case was reported in February 2020 in Lombardy (Northern Italy). Thereafter, it spread vastly and broadly across the country.

Currently, we do not know whether people with MS carry a different risk of SARS-CoV-2 contagion and developing serious complications when infected, especially if exposed to immunomodulatory therapies.

In this paper, we report two cases of MS patients on fingolimod treatment that were infected with SARS-CoV-2 but did not develop any COVID-19 symptom, sign, or complication. Informed consent was obtained from the subjects.

2. Case presentation: patient 1

2.1. History of multiple sclerosis

In 2005 (at the age of 22) patient 1 reported hypoesthesia in the right side of the body. Thereafter described two other episodes characterized by sensory impairment. In 2006 the patient was diagnosed with MS and started therapy with interferon-beta 1a, which was substituted with natalizumab in 2007 due to another sensory relapse and increased lesion load in brain MRI. In 2010, due to PML risk, patient 1 decided to stop current treatment and switched to fingolimod, initiated in 2011 and continued until today. From then on, patient 1 has been free from relapses and MRI has detected no new inflammatory lesion. In January 2020 Expanded Disability Status Scale (EDSS) was 2.5, total lymphocytes 0.68 10^3/mul [normal range between 0.8 10^3/mul and 4.2 10^3/mul].].

2.2. SARS-CoV-2

By end of February 2020, a few days after the first case of COVID-19 in Italy, patient 1 was exposed to COVID-19 cases. Accordingly, the patient was submitted to nasopharyngeal swab specimen that was positive for SARS-CoV-2 using quantitative reverse transcriptase–polymerase chain reaction targeting the RdRp-gene. In accordance to the Italian Society of Neurology (SIN) recommendations, fingolimod treatment was stopped. After appropriate quarantine, two repeated swab tests were negative, while serology was positive [Ab anti SARS-CoV-2 (S1/S2) IgG (CLIA) 23.7 UA/mL (<12)]. A careful clinical follow-up was applied but neither sign, nor symptom evocative either for COVID-19 or for MS clinical activity has been reported, up to the time of their last neurological visit (June 16th). Fingolimod treated has been restarted. but neither sign, nor symptom of COVID-19 nor of MS clinical activity has been reported, up to the time of their last neurological visit (June 16th)

3. Case presentation: patient 2

3.1. History of multiple sclerosis

In 1997 (at the age of 26) patient 2 had an optic neuritis. In 2001 the patient reported a second neurological episode characterized by numbness of right face, thus was admitted to the hospital and diagnosed with MS. After a third neurological episode (diplopia), patient 2 was prescribed glatiramer acetate 20 mg daily. Due to the increased cerebral lesion load, in 2012 patient 2 was switched to interferon-beta 1a. In

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June 2019, due to clinical (gait ataxia) and radiological MS activity, interferon was substituted with fingolimod that was continued until today. From then on, patient 2 has been free from relapses and MRI has detected no new demyelinating lesion. In January 2020 EDSS was 2.5 and total lymphocytes was 0.50 10^3/mul [normal range between 0.8 10^3/mul and 4.2 10^3/mul].

3.2. SARS-CoV-2

In mid-March, patient 2 was exposed to COVID-19 cases. Accordingly, the patient underwent nasopharyngeal swab test for SARS-CoV2 and resulted positive. Following SIN recommendations, patient 2 was advised to interrupt fingolimod treatment. After appropriate quarantine, two repeated swab tests were negative, while serology was positive [Ab anti SARS-CoV-2 IgG (CLIA) 10.82 UA/mL (<0.9)]. A careful clinical follow-up was applied, but neither sign, nor symptom evocative either for COVID-19 or for MS clinical activity has been reported, up to the time of their last neurological visit (May 27th). Fingolimod treated has been restarted.

4. Discussion

SARS-CoV-2 pandemic is fostering uncertainty for patients with MS undergoing immune therapies, potentially exposing them to the risk of infection and severe complications. In addition, the management of disease modifying treatment (DMT) for MS during COVID-19 emergency is conditioned by uncertainties: whether to start, continue, suspend a DMT, and which types of DMT should be preferred.

As per today, the course of COVID-19 in MS patients on fingolimod has been described in at least five other cases: two from USA (Bowen et al., 2020), one from Germany (Foerch et al., 2020), one from Iran (Barzegar et al., 2020) and one from Italy (Chiarini et al., 2020). In detail, the two American and the Italian cases were reported with mild COVID-19 and fully recovered; while the German and the Iranian cases were reported with initially severe COVID-19 requiring admission to intensive care unit; although they had negative prognostic features, they promptly recovered. As the aforementioned five cases, also our two cases have been infected by SARS-CoV-2 but, despite the lymphopenia and the ongoing treatment with fingolimod, they did not develop any sign or symptoms for COVID-19.

Of note, once disclosed SARS-CoV-2 infection, fingolimod treatment had been interrupted, both in our cases and in the published ones. However, the elimination half-life is 4–9 days and the lymphopenia last up to 1–2 months from drug withdrawal, thus fingolimod action likely persisted during the active phase of SARS-CoV-2 infection.

In summary, MS patients on fingolimod treatment who were infected by SARS-CoV-2 had asymptomatic COVID-19, mild COVID-19 or severe COVID-19 but with a surprisingly rapid recovery. This favorable COVID-19 course, might be partially explained by the fact that all affected individuals were relatively young, which is a good prognostic feature (Kronbichler et al., 2020; Oran and Topol, 2020) . Of note recent papers have highlighted that asymptomatic cases are more frequently young and female (Meng et al., 2020; Peckham et al., 2020).

So far, the use of fingolimod does not seem to expose people to a particular risk of unfavorable COVID-19 evolution. Conversely, fingolimod may even have a protective effect against SARS-CoV-2, both enhancing lung endothelial cell integrity and preventing the reactive cytokine storm thanks to the moderate immunosuppression (Ramanathan et al., 2020). An exploratory study to evaluate the efficacy of fingolimod for COVID-19 is undergoing (https://clinicaltrials.gov/ct2/show/NCT04280588).

In addition, notwithstanding the low circulating lymphocytes, in fingolimod immunosuppressed patients, T and B cells in the lymphonode may rapidly expand and mount an effective immune response that favors COVID-19 recovery after drug discontinuation (Chiarini et al., 2020). Note that, after discontinuation of fingolimod, there is a risk of MS relapse due to a 'rebound' effect (Barry et al., 2019), thus longer fingolimod treatment suspension should be avoided.

Based on the above reported experiences, fingolimod therapy is likely safe therapy during COVID-19 outbreak.

Although we could argue that continuing fingolimod during in all COVID-19 cases would reasonable, a very recent paper has reported that the onset of COVID-19 symptoms could be delay up to 4 days (range 3–5) in swab SARS-CoV2 positive asymptomatic individuals (Arons et al., 2020). Thus, in accordance to the international consensus statement (Amor et al., 2020; Giovannoni et al., 2020), fingolimod should be continued in MS patients but might be stopped in SARS-CoV-2 confirmed cases.

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Declaration of Competing Interest

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