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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Mild COVID-19 symptoms in a patient with multiple sclerosis in uninterrupted treatment with fingolimod

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ABSTRACT

Introduction: The use of fingolimod as a long-term therapy in people with Multiple Sclerosis (PwMS) is associated with a small increase in the risk of herpes virus reactivation and respiratory tract infections. At the moment, the outbreak of the novel coronavirus SARS-CoV-2 brings new challenges to physicians when deciding to continue or stop the treatment with fingolimod.
Objective: We report one MS patient tested positive for SARS-CoV-2 that has not discontinued fingolimod treatment and developed only mild symptoms from COVID-19. Methods: Descriptive observational study.
Discussion and conclusion: The effects of COVID-19 infection on MS patients treated with fingolimod are still uncertain. This case report outlines promising results by demonstrating a patient who didn't stop the fingolimod treatment during COVID-19 infection and developed only mild symptoms. Nevertheless, more studies are necessary to evaluate the risks and benefits of fingolimod in MS patients infected with COVID-19.

1. Introduction

The current outbreak of the novel coronavirus SARS-CoV-2 (coronavirus disease 2019; previously 2019-nCoV), epi-centered in Hubei Province of the People's Republic of China, has spread to many other countries. On 30 January 2020, the WHO Emergency Committee declared a global health emergency based on growing case notification rates at Chinese and international locations (Velavan & Meyer, 2020). The most frequent symptoms during illness were cough, fatigue, fever, headache and muscle ache (Boddington et al., 2020).

It has previously been established that people with MS (PwMS) have an increased risk of infections compared with the general population. These infections can lead to significant morbidity and may also contribute to relapses and a worsening of neurological symptoms (Willis & Robertson, 2020).

Fingolimod is a drug used for MS that induces a redistribution of lymphocytes subsets causing an acquired lymphopenia that apparently do not compromise immunosurveillance, although cases of viral (especially varicella zoster) and bacterial infections have been described in real life settings (Grebenciucova & Pruitt, 2017 Sep 22). When the drug is withdrawn, patients may suffer an exacerbation because of the lack of therapeutic coverage, or due to clinical variability (Voskuhl, 2016). The effect of the withdrawal of this drug in patients infected with SARS-CoV2 is not known (Gomez-Mayordomo et al., 2021 Jan).

In this paper, we report a case of one MS patient on fingolimod treatment that was infected with SARS-CoV-2, did not discontinued fingolimod and has developed just mild symptoms of COVID-19 with low fever, headache, fatigue and anosmia. The patient signed the free and informed consent form.

2. MS course

In 2013 (at age of 24) the patient reported seeing double vision followed a few days later by a second neurological episode characterized by weakness on the right leg. Thus, was admitted to the hospital and diagnosed with RRMS MS. The patient started therapy with interferon-beta 1b, which was substituted with fingolimod 0,5 mg per day in 2014 due to elevated side effect and increased cerebral lesion load. From 2015 to 2016 (approximately 11 to 12 months) at the option of the patient himself, treatment with fingolimod was interrupted. With new relapses, fingolimod treatment was returned in 2017 and was continued until today. From then on, the patient has experienced just mild symptoms and MRI has detected no new demyelinating lesion. The EDSS scale has been stable at 1.0 since 2017. The lymphocyte count has also been stable in the last years, in December 2019 it was 0.62 10^3/ml, in March 2020 it was 0.66 10^3/ml and in September 2021 it was 0.68 10^3/ml.

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3. Clinical report

On March 1, 2021, the patient began to feel fatigued and had a temperature rise to 37.2 °. As the patient has been exposed to COVID-19 cases, it underwent a nasopharyngeal swab test for SARS-CoV-2 that resulted positive. Treatment with fingolimod was maintained due to the believe that the medication would not interfere with the course of the COVID-19 infection. At the time of infection, the patient was not yet vaccinated against SARS-CoV-2. In the following days, just mild symptoms with fatigue, headache, dry cough and anosmia were reported. Oximeter measurement was taken daily and did not get below 97% SpO2. It was not possible to measure the lymphocyte count at the time of the infection because the patient stayed at home in complete isolation during the infection of COVID-19. Ten days after the first symptoms, the patient began to report improvement in taste and smell, being completely asymptomatic fifteen days after the onset of symptoms.

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 (Mallucci et al., 2020).

Several case studies have been described in the literature about the relation of SaRS-CoV-2 and fingolimod (Mallucci et al., 2020, Barzegar et al., Jul 2020, Mallucci et al., 2021, Bollo et al., 2020), where fingolimod was withdraw and the patients, even in the presence of low circulating lymphocytes, were able to mount an effective immune response to SARS-CoV-2. The vast majority of patients had just mild or no symptoms and patients who developed severe COVID-19 had a surprisingly rapid recovery.

The study from (Sullivan et al., Jan 2022) had a larger sample of patients treated with fingolimod who had COVID-19, most of them (140/169; 83%) completely recovered or were recovering, (14/161; 8.7%) were severe and (9/161; 5.6%) were critical cases. The study does not specify whether treatment with fingolimod was continued or discontinued at the time of infection, but it states that the risk of more severe COVID-19 symptoms in patients receiving fingolimod seems to be similar to that reported in the general population and the MS population with COVID-19.

Our Study reports a single case only, but it presents promising results that raise the discussion about the effects of not discontinuing fingolimod in patients who are infected with COVID-19.

In COVID-19 patients the severity of the disease depends on the increase of pro-inflammatory factors (Zhang et al., 2020). High levels of several cytokines were significant associated with severe COVID-19 (Li et al., 2020). Thus, blocking the biological activities of cytokines may be beneficial for COVID-19 (TASAT & YAKISICH, 2021 Jan; 21). Fingolimod phosphate initially activates lymphocyte S1P1 via high-affinity receptor binding, yet subsequently induces S1P1 down-regulation that prevents lymphocyte egress from lymphoid tissues, thereby reducing autoaggressive lymphocyte infiltration into the central nervous system (CNS). It might be that in this case, the immunomodulatory function of fingolimod lead to mild COVID-19 infection.

Similar results were found in the study of (Mohammadpour et al., 2021). The authors report a clinical case of a 40-year-old woman who had COVID-19 infection and did not discontinue treatment with fingolimod. The outcome was similar of our patient, having only mild symptoms that improved after 15 days.

Curiously, one study (Gomez-Mayordomo et al., 2021 Jan) described a case study with a patient who developed a mild and long-lasting course of COVID-19. Initially, fingolimod was not discontinued, but was later interrupted due to severe lymphopenia. The patient progressed with respiratory insufficiency and bilateral pneumonia with signs of hyperinflammation syndrome. PCR for SARS-CoV-2 remained positive even 30 days after the first signs of infection, being consistent with a delayed clinical exacerbation of COVID-19 disease, 1 month after disease onset and coinciding with fingolimod discontinuation. The authors discuss that fingolimod may have played a protective role, leading to a milder course of the disease.

Another factor that must be taken into account is that the elimination half-life of fingolimod is 4 - 9 days and the lymphopenia can last up to 1 - 2 months from drug withdrawal, thus fingolimod action is likely to be persistent during the active phase of SARS-CoV-2 infection (Mallucci et al., 2020).

In conclusion, this case study suggests that treatment uninterrupted with fingolimod in MS patient tests positive for SARS-CoV-2 is possibly safe. However, further studies are needed, and the ultimate decision should be individualized through discussion between physician and patient.

Declaration of Competing Interest

The authors report no disclosures. The authors have read the Journal's position on issues involved in ethical publication. There was no sponsorship for the scientific article and there was no conflict of interest with all the authors.

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