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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Covid-19 in a patient with multiple sclerosis treated with natalizumab: May the blockade of integrins have a protective role?

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ABSTRACT

The disease caused by the new coronavirus SARS-CoV-2 (COVID-19) is currently spread worldwide .

Recent data supports SARS-CoV-2 may use integrins to enter human cells. Therefore, anti-integrins therapies might be an alternative against the infection .

Natalizumab, approved for Multiple Sclerosis (MS) treatment, acts blocking α4-integrin.

We report a MS patient treated with natalizumab who develops COVID-19, with excellent recovery and repeated negative results in 5 consecutive microbiological studies. We postulate this may be due to the blockade of integrins induced by natalizumab.

1. Introduction

The disease caused by the new coronavirus SARS-CoV-2 (COVID 19) has become a pandemic, affecting people worldwide (Zhou et al., 2020). It represents a challenge for neurologists treating Multiple Sclerosis due to the concern about how immunosuppressed patients would respond in case of infection. According to this, recommendations have been proposed for the different disease modifying therapies (DMTs) used for MS treatment. In the case of natalizumab, using the extended interval dosing of 6–8 weeks (already described for lowering the risk of Progressive Multifocal Leukoencephalopathy) has been proposed for decreasing the risk of infection and the number of visits to the hospital during the pandemic (Brownlee et al., 2020; Borriello and Ianniello, 2020).

Natalizumab is a humanized monoclonal antibody against α4-integrin used in MS and Crohn's disease.

It is well known that SARS-CoV-2 uses the angiotensin converting enzyme II (ACE2) to enter human cells (Zhou et al., 2020). Although it is just a preliminary hypothesis**,** recent publications suggest SARS-CoV-2 may also use integrins as cell receptors. According to this, drugs that block integrins (such as natalizumab or tirofiban) may be an alternative in COVID-19 treatment (Sigrist et al., 2020; Tresoldi et al., 2020) .

We report a MS patient treated with natalizumab who develops COVID-19, with excellent recovery and repeated negative results in 5 consecutive microbiological studies. We postulate this may be due to the blockade of integrins induced by natalizumab. Furthermore, our case report supports the use of extended interval dosing of natalizumab in selected patients.

2. Case report

An 18 year-old man, with no past medical history, diagnosed with MS in 2013. He initially received Interferon-β1a, switched to dimethyl fumarate in 2015 due to lack of efficacy. In October 2019 he was started on natalizumab due to clinical and radiological activity. Neurological examination showed only minimal signs, EDSS score was 1.5.

At the end of March, patient's mother, with whom he lives, had symptoms suggestive of COVID-19. However, taking into account the patient was asymptomatic and the risk of MS rebound associated to natalizumab discontinuation, treatment was administered on March 30.

On April 2, he presented with fever, cough and malaise. Chest x-ray showed bilateral ground glass opacities suggestive of viral pneumonia. Blood test revealed only slight elevation of fibrinogen (602 mg/dL) and reactive-C-protein (4.26 mg/dL). IL6 was low (2 pg/mL). RT-PCR for SARS-CoV-2 performed on nasopharyngeal swab was negative.

Despite this, given high clinical suspicion of COVID-19, treatment with hydroxychloroquine and azithromycin was administered. A new RT-PCR for SARS-CoV-2 on nasopharyngeal swab and serological test (IgM/IgG) were performed on April 3; both were negative. Microarray for other possible virus affecting the respiratory tract was also negative.

Taking into account epidemiological background in Madrid, typical symptoms and chest-X-ray findings, from 4th to 8th April, three other RT-PCR for SARS-CoV-2 on nasopharyngeal swab were performed. Only the last one was positive (fifth sample taken, 7 days from symptoms onset).

Patient completely recovered within a week, with no abnormalities in blood tests. He was discharged to home-quarantine on April 10. No respiratory or neurological symptoms have been reported since then. Antibodies against SARS-Cov-2 were detected on May 7. PCR on nasopharyngeal swab was double-negative then. Natalizumab was administered on May 11, six weeks after the previous one, according to the extended interval dosing proposed to prevent infectious complications, without any incidence.

3. Discussion

Patients with MS, especially those receiving immunosuppressants, have higher risk of infection. Nevertheless, in SARS-CoV-2 disease, it has been postulated that previous use of immunosuppressive drugs could provide a protective mechanism against the most severe phase of the disease, caused by cytokine release and hyper-inflammatory state that can lead to acute respiratory distress syndrome and even death (Mehta et al., 2020).

Natalizumab is a humanized monoclonal antibody against α4-

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integrin used in MS and Crohn's disease. Integrins are heterodimeric cell surface receptors that play a role in cell adhesion, migration and signaling processes (Sigrist et al., 2020). Through its action blocking α4-integrin, natalizumab avoids lymphocyte and monocyte cell adhesion and transendothelial migration. Its efficacy in MS is well known.

The angiotensin converting enzyme II (ACE2) is a cell receptor used by SARS-CoV-2 (Zhou et al., 2020). Previous reports describe how viruses use the RGD or non RGD domains for infection (Hussein et al., 2015). Although it is just a preliminary hypothesis and there is no data focused on α4-integrin, recent publications suggest SARS-CoV-2 may also use integrins as cell receptors binding to them through a conserved RGD motif. This domain is present in the receptor-binding domain of the spike proteins of SARS-CoV-2, allowing the virus to enter human cells and to start viral replication. The RGD motif is the minimal peptide sequence required for binding proteins of the integrin family, which are commonly used as receptors by many human viruses, such as adenovirus or metapneumovirus. The conservation of the motif and its localization in the receptor-binding region of the SARS-CoV-2 spike protein suggests that integrins may be alternative receptors for this virus. It has been proposed that binding to integrin may play a supplemental role to ACE2 binding. Alternatively, the virus could infect different cells by binding to ACE2 or to integrins. According to this, drugs that block integrins (such as natalizumab or tirofiban) may be an alternative in COVID-19 treatment (Sigrist et al., 2020; Tresoldi et al., 2020).

Our patient had received natalizumab 48 h before symptoms onset, with the consequent block of α4integrin. If, as it has been proposed, SARS-CoV-2 may enter human cells through integrins, the blockade of these receptors by natalizumab may explain a low viral replication rate that could cause the repeated negative results for PCR for SARS-CoV-2, as well as a benign course of the disease.

Initial negative serological results may be due to low production of antibodies associated with low viral replication or previous immunosuppression. It could also be because they were tested in the window period, at the very beginning of the disease.

As far as we are concerned, this is the second case published of COVID-19 in a patient with MS treated with natalizumab with good outcome (Borriello and Ianniello, 2020).

Even more relevant, it is the first report that suggests the possible role of natalizumab in preventing SARS-CoV-2 from binding to some of its receptors. This theory might open the possibility of using integrins blockade as a therapeutic alternative against SARS-CoV-2 infection.

Moreover, this case supports the use of natalizumab extended interval dosing in selected patients in order to decrease the risk of infection as well as the possible MS rebound if natalizumab is discontinued. The good response of this individual is consistent with recovery in other studies (Borriello and Ianniello, 2020; Sormani et al., 2020).

Declaration of Competing Interests

The Authors declares that there is no conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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