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Case report

COVID-19 occurring during Natalizumab treatment: a case report in a patient with extended interval dosing approach

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ABSTRACT

Background: The novel Coronavirus SARS-CoV-2, which was identified after a recent outbreak in Wuhan, China, in December 2019, has generated a global pandemic impacting over 200 countries around the world. Recent reports suggest that ACE2, which is the target protein to invade the host, has a ubiquitous presence in human organs, including lung parenchyma, gastrointestinal tract, nasal mucosa, renal and urinary tract, airway epithelia, lymphoid tissues, reproductive organs, vascular endothelium and neurons. In this scenario, neurologists are particularly involved into considering even more specific therapeutic strategies according to the available data during the pandemic. In particular, MS patients are usually receiving disease-modifying therapies (DMTs) with immunosuppressant or immunomodulatory effects, which increase the risk of infections and morbidity, compared with the general population. Development of PML or other serious opportunistic infections during treatment with natalizumab forces to consider whether de-risking strategies are needed in this particular context and how to manage a high-efficacy treatment.

Methods: In this paper we report on a patient treated with natalizumab for relapsing MS who developed COVID-19 and recovered in a few days without complications.

Results: After recovery natalizumab has been administered in the window of the extended interval dosing (EID), without reporting any worsening or new symptoms.

Discussion: This case supports the opportunity to avoid discontinuing or delaying the retreatment over 8 weeks in patients recovered from a recent COVID-19.

The major clinical manifestation of Coronavirus disease 2019 (COVID-19) infection is an interstitial pneumonia with different phenotypes, the most severe consisting in acute respiratory distress syndrome, typically followed by disseminated intravascular coagulation (DIC) and fatal multi organ failure (MOF) (Zhu et al., 2020). SARS-CoV-2 is thought able to invade CNS through the olfactory bulbs epithelium, which shows a higher expression of the protein hACE2, the receptor identified as the one used to gain entry into the host (Zhu et al., 2020), or carried into the brain by the blood, with subsequent infection of vascular endothelium or macrophages. Many factors have drawn the attention of neurologists: a significant number of cases of altered mental status and other neurological symptoms like anosmia and ageusia (Huang et al., 2020). The first report of acute necrotizing encephalopathy (ANE), a rare complication of influenza and other viral infections, in a COVID positive female patient, has increased even more the alert in the neurological community (Poyiadji et al., 2020). This issue sounds relevant in particular for patients treated with immunosuppressant drugs. In Multiple Sclerosis (MS), prolonged treatment with natalizumab can reduce immune surveillance in the CNS, increasing the risk that poliomavirus JC could establish a lytic infection in oligodendrocytes, leading to Progressive Multifocal Leukoencephalopathy (PML). To limit the onset of this peculiar adverse event we adopted strategies to mitigate the risk, such as dosing of natalizumab in a less frequent range (extended interval dosing-EID) of 6-8 weeks, differently from the approved treatment schedule of every 4 weeks (standard interval dosing-SID) (Clerico et al., 2020).

We report a case of COVID-19 in a patient with MS treated with the monoclonal antibody natalizumab (humanized anti-VLA4), a 28-year old Caucasian health worker male (118 emergency ambulance driver). He received the diagnosis in the year 2000, when he developed acute upper and lower limb hyposthenia on the left side. Nothing relevant appears in his past medical history. He was previously treated with

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dimethyl fumarate and has always tested JCV-negative. At the end of February 2020, he underwent his 14th infusion in an EID regimen at 6 weeks. Routine haematological screening resulted in normal peripheral blood lymphocyte count; renal and hepatic function parameters were in the normal range. Expanded disability status scale (EDSS) was 1.5. On March 11 he developed a fever (38,6°C), no other symptoms. PCR on nasal swab resulted positive for SARS-CoV-2 on two consecutive samples. He was admitted to Spallanzani Hospital in Rome on March 19, due to persistent high fever and the emergence of dyspnoea. Chest CT showed mild bilateral interstitial pneumonia with ground glass opacities and arterial blood gas test showed normal blood oxygenation. Patient was treated with antipyretics, hydroxychloroquine and antibiotics, with resolution of symptoms within 10 days. He was discharged home on the 1st of April after double-negative swabs. Patient returned to our hospital for treatment infusion at 7 weeks, still in the window of the EID. Blood exams showed normal leucocyte and lymphocyte count (5.68 × 10^9 cells/L, range 4.00-10.00 and 2.17 × 10^9 cells/L, range 1.00-4.50, respectively), with normal C-reactive protein (0,4 mg/L, range 0-5) and a slight increase of fibrinogen (467 mg/dl, range 150-450). At 2 weeks from the last administration, the patient is still at home due to the institutional lockdown, without the onset of any new symptoms or worsening of previous clinical conditions. Most notably, he hasn't developed any respiratory symptoms. To our knowledge, this is the first reported case of a natalizumab treated patient developing COVID-19, recovered and then retreated, without short-term complications.

Although natalizumab potentially blocks viral immunosurveillance of the CNS, PML is a rare event: approximately a total of 765,985 patient-years has been exposed globally in the post approval setting, with overall PML incidence of 4.08 per 1,000 (95% CI, 3.80-4.36 per 1,000 patients). EID has been suggested to reduce significantly PML risk compared to SID (Clerico et al., 2020). At the time being, it is unknown if natalizumab could potentially be a risk factor for a severe PML-mimicking Neuro-COVID encephalopathy, whereas the risk of recurrence of disease activity when discontinuing natalizumab is deeply documented (Fox et al., 2014). Arising data on SARS-CoV-2 neurotropism and about how the virus may be carried into the CNS will mitigate or clarify present concerns.

Declaration of Competing Interest

The authors report no conflict of interest.

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