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CASE REPORT

SARS-CoV2 Infection in a Multiple Sclerosis Patient Treated with Natalizumab – A Case Presentation

Georgiana Șerban*, Rodica Bălașa

George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania

Introduction: The novel coronavirus, SARS-CoV2, has rapidly spread worldwide and led to an intense collaboration among both physicians and researchers in order to stop its dissemination. Little is yet known about how this virus behaves, but recent studies have suggested the role of integrins in the viral penetration of target cells. Natalizumab is an anti-α4-β1 integrin monoclonal antibody used in the treatment of multiple sclerosis (MS), a neurodegenerative auto-immune disease affecting primarily young adults. MS patients have a greater susceptibility to develop severe infections especially enhanced by the disease-modifying therapies (DMTs) which are currently recommended for their treatment. Natalizumab is considered the safest high-efficacy DMT in times of COVID-19 outbreak. **Case presentation**: We hereby describe the first case from Romania of a MS patient treated with Natalizumab who subsequently acquired SARS-CoV2 infection and whose recovery was excellent, with no functional neurological or respiratory sequelae. **Conclusion**: The favourable evolution of our patient supports the potential therapeutic effect Natalizumab might have in SARS-CoV2 treatment by specifically blocking integrins and by its immunosuppressant characteristics.

Keywords: multiple sclerosis, Natalizumab, SARS-CoV2 infection, COVID-19 outbreak

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Introduction

The entire medical community has been shaken by the incredibly rapid dissemination and the brutal behaviour of the novel coronavirus that first appeared in Wuhan, China in December 2019. SARS-CoV2 is a beta-coronavirus that predominantly affects the respiratory system, but in severe cases can have a broader spectrum of symptoms, from cutaneous to neurological manifestations [1]. The most prone to develop severe forms of infections are the elderly, people having important comorbidities (e.g. cardiovascular disease, diabetes) and those treated with immunosuppressant drugs [2].

Multiple sclerosis (MS) is a major debilitating neurological disease mainly affecting young adults. Its treatment has widely developed in recent years. Nowadays, the long-term standard therapy consists of disease modifying therapies (DMTs), while the relapses are managed with corticosteroids. Several studies have demonstrated that not only are MS patients predisposed to contract severe forms of infections, but also DMTs increase their susceptibility [3]. The stronger potency the drugs have, the higher the vulnerability they induce [4]. Therefore, the ongoing COVID-19 pandemic has imposed a series of precautions regarding DMTs administration that neurologists should take into account.

Natalizumab is an anti-α4-β1 integrin monoclonal antibody which inhibits the lymphocytes transmigration into the inflamed central nervous system and, consequently, diminishes the immune surveillance of the brain [4,5]. It is considered the safest high-efficacy DMT used in times of SARS-CoV2 pandemic. Extending the dosing interval (EDI) to 6-8 weeks instead of a monthly administration has lately been proposed as a tactic to avoid the occurrence of progressive multifocal leukoencephalopathy (PML). This could also be beneficial during this outbreak by decreasing the number of visits to the hospital and, therefore, the risk of contracting the infection. In addition, novel studies suggest the potential involvement of integrins in coronavirus invasion and, thus, Natalizumab might be considered a helpful alternative for COVID-19 treatment [6].

We report the case of a young adult diagnosed with MS and treated with Natalizumab who subsequently acquired a COVID-19 infection, with favourable evolution and excellent recovery. To our knowledge, this is the first case of MS patient treated with Natalizumab contracting SARS-CoV2 infection from Romania.

Case Presentation

We hereby report the case of a 45-year male adult diagnosed with MS in 2013, when he presented lower limbs paresthesias and motor deficit. He initially received interferon beta-1a until October 2018, with repeated relapses. The treatment was switched to Natalizumab in December 2018 and the patient received the perfusion on a monthly basis. The last administration of Natalizumab was on the 5th of June 2020, when the haematological screening showed a slight leucocytosis (10820/mm3) with neutrophils and lymphocytes values within normal range, unmodified kidney and liver function. Neurological examination did not show any aggravation of his deficits in comparison with former examination, Extended Disability Status Scale (EDSS) score was 5.5 points.

* Correspondence to: Georgiana Șerban
E-mail: georgiana.serban94@yahoo.com

On the 1st of July 2020, the patient presented subfebrile temperature, dry cough, headache and arthralgia. The following day, he sought medical advice to his general practitioner on whose recommendation he was admitted to Infectious Disease Clinic. The first RT-PCR on the nasopharyngeal swab, performed on the 2nd of July, revealed a positive result for SARS-CoV2 infection. At the moment of admission, the standard blood and urine analyses were within normal values. D-dimers were elevated. The clinical status of the patient was rather good, with normal blood pressure and no signs of dyspnea. The chest X-ray showed no pathological modifications. Patient was treated with Kaletra (lopinavir/ritonavir) for 10 days, dexamethasone for 14 days, ceftriaxone and doxycycline for 7 days, associated with gastric protectors and low-molecular-weight heparin.

During the first week of hospitalisation, the number of WBC gradually increased, revealing slight neutrophilia and insignificant lymphopenia. The liver enzymes suffered a steady rise as well. The remaining parameters were unmodified. The chest CT performed 8 days from admission revealed bilateral ground glass opacities, occupying less than 25% of the lungs. The pulmonary X-ray was similar to the previous one. A second RT-PCR test still revealed a positive result.

Nonetheless, the blood analysis slowly normalised within the second week. Before patient's discharge, D-dimers became negative and feritin was double its previous value (1099.5 ng/ml)). Three more RT-PCR tests were performed, showing positive result for COVID-19 infection. According to serological analysis from 18th of July, the patient had positive IgG antibodies and negative IgM antibodies against SARS-CoV2. The chest X-ray performed before discharge showed alveolar opacities in the left lung base.

The evolution was favourable, with normal temperature, no signs of respiratory failure and resolution of former symptomatology. He was discharged home after 16 days of antiviral, antibiotic and anti-inflammatory treatment and isolation.

On the 23rd of July, three weeks after the occurrence of initial symptoms, the patient had a medical check-up. He presented no SARS-CoV2-associated signs and symptoms, normal blood pressure, respiratory rate, oxygen saturation and temperature. The haematological screening revealed slight modifications related to inflammatory markers: CRP 1.23 mg/dl, ESR 20 mm/h, feritin 399.2 ng/ml. The remaining parameters were within normal range. The control chest X-ray revealed bilateral focal interstitial lesions in the lung bases.

The patient was scheduled for Natalizumab administration on 5th of August, 8 weeks and 5 days after the previous cure, exceeding the EDI protocol intended to prevent further infectious complications. Nonetheless, the neurological status was influenced neither by infection, nor by the delay in Natalizumab administration.

Discussion

SARS-CoV2 is characterised by impressive spreading velocity and high virulence, features that transform the novel coronavirus into a serious public health concern. For this pandemic to happen, the virus has to penetrate the cells in order to replicate. Therefore, the virus interaction with the recipient cells is currently of great interest to understand the viral pathogenicity.

Zhou et al [7] have already demonstrated the role of ACE2 receptor in the virus transmission. The current focus is on integrins, cell surface receptors widely expressed throughout the body and involved in cells adhesion, migration and signalling pathways [6]. Previous studies demonstrated that other viruses (adenovirus, Ebstein-Barr virus, cytomegalovirus – to name a few) use integrins to invade the cells. In order to do so, it is mandatory for the virus to present a specific sequence of peptides, called RGD-motif, whom the integrins use to bind. Sigrist et al [6] suggested the aforementioned relationship as an alternative explanation for SARS-CoV2 pathogenesis. Non-RGD binding integrins are also proposed to be involved in coronavirus invading process [8]. Agguire et al [9] suggested that the integrin-based mechanism could be salutary to ACE2 receptor-mediated invasion. Furthermore, the viral ability to penetrate the cells via two different pathways implies a wider diversity of target cells [9]. Natalizumab, as a monoclonal antibody against $\alpha 4$-$\beta 1$ integrin, might prove to be a valuable resource for SARS-CoV2 treatment. It is worth mentioning that integrins are found to be overexpressed in inflamed tissues and that their behaviour towards their ligands is highly influenced by the surrounding microenvironment, particularly by cytokines and chemokines [8]. In the future, a new research field could concentrate on the exploitation of molecules capable of interacting with cytokines in order to subsequently manipulate the integrins.

Furthermore, immunosuppressant drugs are currently considered potential therapies to inhibit the cytokine storm specific to SARS-CoV2 infection [10]. Natalizumab blocks vascular cell adhesion molecule one (VCAM-1) which is highly expressed in virally-inflamed lungs and, consequently, impedes monocytes' diapedesis, thus diminishing the damaging effects on pulmonary tissue [4]. On the other hand, Natalizumab decreases central nervous system immune surveillance and, therefore, might raise the risk of COVID-19 encephalitis [11]. In addition, it is recognized for its high susceptibility to upper respiratory tract infections [3,11]. Nonetheless, patients treated with Natalizumab, a non-lymphocyte depleting drug, have a lower risk of developing severe forms of SARS-CoV2 infections, compared with those on B-cell-depleting therapies [12].

Standard interval dosing (SID) defines a monthly administration of Natalizumab. Zhovtis et al [13] demonstrated that extending the dosing interval up to 8 weeks does not influence the drug efficacy and, more importantly, diminishes the risk of developing PML. This strategy is outstandingly beneficial in times of SARS-CoV2 pandem-

ic because it allows reduced contact with the hospital and, consequently, a lesser exposure to the virus [10]. To this date, only two MS patients treated with Natalizumab and subsequently contracting COVID-19 infection have been reported and both of them had a favourable evolution with full recovery [9,14]. Both of them received Natalizumab according to EDI schedule.

Conclusion

SARS-CoV2 pandemic represents a challenging period for the entire population and particularly for patients suffering from chronic diseases. MS patients are likely to contract different kinds of infections especially due to therapy-induced susceptibility. Therefore, their risk of acquiring COVID-19 infection is significantly higher. Natalizumab is considered the safest high-efficacy drug available for MS treatment. A series of hypotheses regarding the potential therapeutic role of Natalizumab in COVID-19 infection has lately emerged due to newly-recognized involvement of integrins in viral penetration of the cells and immuno-suppressive effect of Natalizumab. We therefore presented the case of a patient diagnosed with MS and treated with Natalizumab who subsequently developed SARS-CoV2 infection and whose recovery was excellent, without any functional sequelae, which might emphasize the beneficial effect of this drug during current outbreak.

Authors' Contributions

G.Ş. (Conceptualizaton; Data collection and analyzing; Writing – original draft)
R.B. (Conceptualization; Writing – review and editing)

Conflicts of Interest

The authors declare no conflict of interest.

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