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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Safety of Natalizumab infusion in multiple sclerosis patients during active SARS-CoV-2 infection

ARTICLE INFO

Keywords
Natalizumab
Multiple sclerosis
SARS-CoV-2
Safety

SUMMARY

COVID-19 pandemic represented a challenge in the management of treatments for Multiple Sclerosis (MS), such as Natalizumab (NTZ). NTZ interferes with the homing of lymphocytes into the central nervous system, reducing immune surveillance against opportunistic infection. Although NTZ efficacy starts to decline 8 weeks after the last infusion, increasing the risk of disease reactivation, evidence is lacking on the safety of reinfusion during active SARS-CoV-2 infection. We report clinical outcomes of 18 pwMS receiving NTZ retreatment during confirmed SARS-CoV-2 infection. No worsening of infection or recovery delay was observed. Our data supports the safety of NTZ redosing in these circumstances.

1. Background

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still considered a global health issue, due to its high mortality rate and morbidity burden worldwide. In the past months intense research has been dedicated to understanding whether immune depressed individuals, such as patients with multiple sclerosis (MS) treated with immunosuppressants, may have worse outcomes after COVID-19, compared to healthy subjects.

Many studies have shown that therapies for MS present an acceptable safety profile with no relevant relationship between COVID-19 severe outcomes and disease modifying therapies (DMTs) use, except for anti-CD20 therapies (Sormani et al., 2021; Zabalza et al., 2021; Salter et al., 2021). Nevertheless, the safety of treatment continuation during active infection has not been explicitly explored. This is particularly interesting for drugs with a sequestering mechanism of action, like NTZ, whose suspension is associated with the risk of a time dependent disease reactivation. Infection by SARS-CoV-2, in fact, may last longer than the estimated safety intervals of retreatment (Plavina et al., 2017) posing the question of risk/benefit of infusion in patients with active infection.

There is no consensus on the optimal management of NTZ in such circumstances.

This paper illustrates a case experience of 18 people with Multiple Sclerosis (pwMS), from 6 Italian MS centers, who received NTZ infusion before proving negative to SARS-CoV-2 swab.

2. Methods

We retrospectively collected data from 18 relapsing-remitting pwMS under NTZ treatment, infected by SARS-CoV-2 between October 2020 and May 2021, from 6 Italian MS centers (see Table 1 for demographic and clinical features of the cohort).

Patients were selected according to the following additional criteria:

1) Infection by SARS-CoV-2 between two consecutive NTZ infusions
2) Positive RT-PCR nasopharyngeal swab at the time of NTZ reinfusion
3) Consenting to be infused with NTZ before achieving negative SARS-CoV-2 swab

The following variables were collected and analyzed: baseline demographic, lifestyle, and clinical characteristics of MS (age, disease duration, median EDSS, total NTZ infusion and regimen) and outcomes of SARS-CoV-2 infection (COVID-19 symptoms at onset, at the time of and after reinfusion, date of first positive swab, date of the closest positive swab with respect to NTZ reinfusion, and date of first negative swab).

The descriptive statistical analysis was performed using SPSS program version 23.0

3. Results

All patients included in the study had at least one symptom of COVID-19 at onset; in particular, 72% (13/18) complained of anosmia, 66% (12/18) ageusia, 44% (8/18) fever or myalgias or headache, 38% (7/18) nasal congestion, 33% (6/18) cough and 16% (3/18) sore throat. None of them experienced gastrointestinal symptoms. All of them received NTZ infusion before achieving a negative SARS-CoV-2 molecular swab. One patient was found positive on the day of his first NTZ infusion.

At the time of NTZ reinfusion 6/18 were still symptomatic for COVID-19, while 12/18 were asymptomatic. NTZ was reinfused in a median interval of 48 (0–73) days after the pre-COVID19 infusion and specifically, those on standard interval doses (SID, n = 7) were reinfused after 30 (0–36) days and those in extended interval doses (EID, n = 11) after 54 days (42–73). None of the patients reported worsening of SARS-CoV-2 symptoms or developed new neurological symptoms suggestive of central nervous system (CNS) invasion by SARS-CoV-2 after redosing. Patients still symptomatic at the time of reinfusion presented a mean time to full recovery after NTZ of 10±12 days. For the whole study cohort, the mean interval from first symptoms to NTZ reinfusion was 19±9 days while the mean interval from the first COVID-19 symptom to full recovery was 13±9 days and the mean interval from first positive
likely to the CNS. Additionally, we did not observe any new symptoms affecting the CNS. Furthermore, the partial efficacy may last up to 12 weeks (Plavina et al., 2017).

Gastrointestinal tract which is another target for SARS-CoV-2 infection beyond lung infection, may involve several other organs, including the CNS. CNS invasion may occur through direct infection of the neural cells via disrupted BBB, olfactory pathway or infected immune reservoir cells (Iadecola et al., 2020).

Moreover, damage to the CNS may also be due to systemic hyperinflammatory response to SARS-CoV-2 leading to a secondary cytokine release syndrome (Iadecola et al., 2020). While NTZ reinfusion might limit the risk of disease relapse, consented to be reinfused before achieving a negative swab.

In this study, we selected a special cohort of patients who, in order to limit the risk of disease relapse, consented to be reinfused before achieving a negative swab.

Indeed, after NTZ therapy, no one of our patients experienced any systemic or neurological clinical worsening related to CoV-19, suggesting that NTZ does not facilitate SARS-CoV-2 replication inside the CNS. Additionally, we did not observe any new symptoms affecting the gastrointestinal tract which is another target for both SARS-CoV-2 invasion and NTZ action.

The mean time to symptoms recovery in our cohort was in line with the outcomes observed in the general population (Rhee et al., 2021), meaning that NTZ does not reduce the viral clearance. Moreover, all of our patients had mild COVID-19, and none required oxygen support or hospitalization.

Although this study presents several limitations, the most important being the small sample size and not including severe COVID-19 patients, based on our data, we can conclude that NTZ has no detrimental effect on COVID-19. Conversely, emerging evidence supports the hypothesis that NTZ might even be beneficial in counterbalancing infection by limiting SARS-CoV-2 cells entry via integrin blockade (Aguirre et al., 2020; Sigrist et al., 2020).

In our cohort 7/18 pwMS received the infusion in line with their ordinary schedule, while the majority of them had to postpone the infusion mainly due to difficulties in accessing the MS centers. Nevertheless, our data demonstrate that NTZ reinfusion in positive patients with mild COVID-19 is reasonably safe. When circumstances allow, in order to minimize the risk of MS rebound or possible exacerbation of the COVID-19 itself, we suggest not to delay retreatment.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Funding Source Declaration**

No specific funding for this work

**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103345.

**Bibliography**

Aguirre, C., Meca-Lallana, V., Barrion-Blandino, A., del Río, B., Vivancos, J., 2020. Covid-19 in a patient with multiple sclerosis treated with natalizumab: may the blockade of integrins have a protective role? Mult. Scler. Relat. Disord. 44, 102250 https://doi.org/10.1016/j.msard.2020.102250 https://doi.org/10.1016/j.msard.2020.102250.

Breton, G., 2010. Syndrome inflammatoire de reconstitution immune. Médecine/sciences 26, 281–290. https://doi.org/10.1051/medsci:2010262281 https://doi.org/10.1051/medsci:2010262281.

Iadecola, C., Anrather, J., Kamel, H., 2020. Effects of COVID-19 on the nervous system. Cell 183, 16–27. https://doi.org/10.1016/j.cell.2020.08.028 e1https://doi.org/

Plavina, T., Muralidharan, K.K., Kueters, G., Mikol, D., Evans, K., Subramanyam, M., Nestorov, I., Chen, Y., Dong, Q., Ho, P.-R., Amarante, D., Adams, A., De Seze, J., Fox, R., Gold, R., Jeffery, D., Kappos, L., Montaltan, X., Weinstock-Gutmann, B., Hartung, H.-P., Cree, B.A.C., 2017. Reversibility of the effects of natalizumab on peripheral immune cell dynamics in MS patients. Neurology 89, 1584–1593. https://doi.org/10.1212/WNL.0000000000004485 https://doi.org/10.1212/WNL.0000000000004485.

Rhee, C., Kanjišl, S., Baker, M., Klompas, M., 2021. Duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity: when is it safe to discontinue isolation? Clin. Infect. Dis. 72, 1467–1474. https://doi.org/10.1093/cid/ciaa1249 https://doi.org/10.1093/cid/ciaa1249.
Salter, A., Fox, R.J., Newsome, S.D., Halper, J., Li, D.K.B., Kanellis, P., Costello, K., Bebo, B., Rammohan, K., Cutter, G.R., Cross, A.H., 2021. Outcomes and risk factors associated with SARS-CoV-2 infection in a North American registry of patients with multiple sclerosis. JAMA Neurol. 78, 699. https://doi.org/10.1001/jamaneurol.2021.0688 https://doi.org/.

Sigrist, C.J., Bridge, A., Le Mercier, P., 2020. A potential role for integrins in host cell entry by SARS-CoV-2. Antiviral Res. 177, 104759 https://doi.org/10.1016/j.antiviral.2020.104759 https://doi.org/.

Sormani, M.P., Salvetti, M., Labauge, F., Schiavetti, I., Zephir, H., Carmisciano, L., Bensa, C., De Rossi, N., Pelletier, J., Cordioli, C., Vukusic, S., Moiola, L., Kerschen, P., Radaelli, M., Theaudin, M., Immovilli, P., Casez, O., Capobianco, M., Ciron, J., Trojano, M., Stankoff, B., Créange, A., Tedeschi, G., Clavelou, P., Comi, G., Thouvenot, E., Battaglia, M.A., Moreau, T., Patti, F., De Seze, J., Louapre, C., the Musc-19, the Covisep study groups, 2021. DMTs and Covid-19 severity in MS: a pooled analysis from Italy and France. Ann. Clin. Transl. Neurol. 8, 1738–1744. https://doi.org/10.1002/acn3.51408 https://doi.org/.

Steinman, L., 2014. Immunology of relapse and remission in multiple sclerosis. Annu. Rev. Immunol 32, 257–281. https://doi.org/10.1146/annurev-immunol-032713-120227 https://doi.org/.

Zabalza, A., Cárdenas-Robledo, S., Tagliani, P., Arrambide, G., Otero-Romero, S., Carbó-Net-Mirabent, P., Rodríguez-Barranco, M., Rodríguez-Acevedo, B., Restrepo Vera, J.L., Restrepo-Vera, J.L., René-Salas, M., Madrigal, L., Vidal-Jordana, A., Río, J., Galan, I., Castillo, J., Cobo-Catvo, A., Comabella, M., Noguera, C., Sastre-Garriga, J., Tintore, M., Montalban, X., 2021. COVID-19 in multiple sclerosis patients: susceptibility, severity risk factors and serological response. Eur. J. Neurol. ene. 14690 10.1111/ene.14690 https://doi.org/.