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.
Correspondence

Mild or no COVID-19 symptoms in cladribine-treated multiple sclerosis: Two cases and implications for clinical practice

ABSTRACT

Background: The use of disease-modifying therapies (DMTs) in multiple sclerosis (MS) could affect COVID-19 outcomes by modulating the immune response, which, in turn, might favor viral replication and/or confer protection from COVID-19 induced inflammatory response.

Case report: We report on two MS patients treated with cladribine, with heterogeneous demographics and clinical features, who developed mild or no symptoms from COVID-19 and produced anti-SARS-CoV-2 antibodies, notwithstanding low lymphocyte levels.

Implications: Benign COVID-19 clinical course and anti-SARS-CoV-2 antibody production can occur in MS patients with lymphopenia, suggesting the possibility to respond to COVID-19 vaccination, once available, in this vulnerable population.

1. Introduction

Several initiatives are currently gathering information on the relationship between multiple sclerosis (MS) and coronavirus disease 2019 (COVID-19); still, few data are currently available (Sormani, 2020, Parrotta et al., 2020, Montero-Escribano et al., 2020).

In particular, the use of disease-modifying therapies (DMTs) could affect COVID-19 outcomes by modulating the immune response (i.e., disease specific antibody production, cytokine production), which, in turn, might favor viral replication and/or confer protection from COVID-19 induced inflammatory response (Berger et al., 2020). We hereby report on two MS patients treated with cladribine tablets, with heterogeneous demographics and clinical features, who developed mild or no symptoms from COVID-19 and produced anti-SARS-CoV-2 antibodies, notwithstanding lymphocyte levels below normal values.

2. Case report

A 29-year-old man was diagnosed with relapsing-remitting MS in May 2018; Expanded Disability Status Scale (EDSS) score was 1.5. Due to clinical and radiological activity, he was commenced on cladribine tablets in July 2018. He screened negative for tuberculosis, HIV, hepatitis B and C, cytomegalovirus and varicella-zoster virus. Redosing of cladribine was performed in July 2019. Clinical, radiological and laboratory follow-ups were substantially uneventful. Blood tests before COVID-19 pandemic (January 2020) showed grade 3 lymphopenia (390 lymphocytes/µL), with reduced levels of CD4+ lymphocytes (66/µL), CD8+ lymphocytes (39/µL) and CD20+ lymphocytes (39/µL). In March 2020, while he was in Switzerland, he presented with anosmia, dysgeusia, diarrhea and fever, for which he was quarantined at home without testing. He fully recovered in a few days using paracetamol as needed. In June 2020, he tested positive for SARS-CoV-2 RNA on nasopharyngeal and oropharyngeal swabs, within tracing procedures of COVID-19 positive subjects. She did not present with any symptoms and tested negative on two following swabs in June 2020. In July 2020, she tested positive for anti-SARS-CoV-2 IgG antibodies on both LFIA and CLIA.

A 61-year-old woman with concomitant hypertension and dyslipidemia, was diagnosed with relapsing-remitting MS in July 1994; EDSS was 2.5. She was initially treated with interferon beta1a, and, then, due to disease activity, switched to fingolimod in January 2017, and to cladribine in December 2019 (first year dosing was completed in January 2020). Blood tests before COVID-19 pandemic (February 2020) showed grade 1 lymphopenia (860 lymphocytes/µL). In May 2020, she tested positive for SARS-CoV-2 RNA on nasopharyngeal and oropharyngeal swabs, within tracing procedures of COVID-19 positive subjects. After testing positive for SARS-CoV-2 RNA, she was isolated at home for 14 days. Blood test before isolation showed grade 2 lymphopenia (620 lymphocytes/µL).

3. Discussion

Reduction of peripheral lymphocytes is expected during cladribine treatment. However, cladribine is a relatively poor T-cell depleting agent, and holds low risk of viral infections (Stuve et al., 2019). Accordingly, in the phase 3 CLARITY study viral infections were uncommon and mild or moderate in severity (Cook et al., 2011). It is currently unknown whether lymphopenia represents a risk factor for morbidity and mortality from COVID-19, or is actually beneficial by preventing the abnormal systemic immune response (Parrotta et al., 2020, Minotti et al., 2020). We have shown that MS patients with lymphopenia following cladribine treatment can develop mild or no symptoms from COVID-19, suggesting that lymphopenia is not necessarily a risk factor for worse disease outcomes, and immunosuppressive DMTs do not necessarily need to be suspended or delayed in the course of the current pandemic (Giovannoni et al., 2020, Buonomo et al., 2020). This consideration applies to both a young, newly-diagnosed, drug-naïve patient and to an adult patient with comorbidities and long standing history of MS clinical features and treatments. Another relevant point is that patients treated with immunosuppressive DMTs, when infected, can present with mild or no COVID-19 symptoms and, being underdiagnosed, they might become an important source for viral spreading (Minotti et al., 2020). As such,
MS centers should carefully put into effect screening procedures (COVID-19 testing) while promoting social distancing and the use of individual protection devices for all consultations (e.g., face masks).

Our cases also suggest that MS patients with lymphopenia following cladribine treatment can develop anti-SARS-CoV-2 antibodies. This result was confirmed by two different serological tests to increase sensitivity and specificity (Lisboa Bastos et al., 2020), and has definite implications for the possibility to respond to COVID-19 vaccination, once available, in this vulnerable population.

We acknowledge that the generalizability of our considerations is limited, deriving from the observation of two isolated cases, but we believe that they represent valuable hints needing confirmation in larger populations. Also, while COVID-19 testing for all MS patients dosing/redosing immunosuppressive DMTs has been suggested (Buonomo et al., 2020), there are differences between healthcare systems and local protocols that should be accounted for when translating our considerations in clinical practice.

In conclusion, our two patients with cladribine-induced lymphopenia, presented with mild or no COVID-19 symptoms, quickly recovered, and were able to develop anti-SARS-CoV-2 antibodies. While there is no evidence for the effects of cladribine and other DMTs on COVID-19, our cases suggest that benign clinical course and antibody production also occur in MS patients with lymphopenia.

Declaration of Competing Interest

Marcello De Angelis has nothing to disclose. Maria Petracca has received honoraria from Biogen, Teva, Genzyme, Merck, Novartis, Almirall. Vincenzo Brescia Morra has received honoraria from Biogen, Teva, Genzyme, Merck, Novartis, Almirall. Marcello Moccia has received research grants from ECTRIMS-MAGNIMS, UK MS Society, and Merck; honoraria from Biogen, Merck, Novartis, and Roche; and consulting fees from Veterans Evaluation Services.

Disclosures

Authors report no disclosures relevant to the manuscript.

References

Sormani, MP., 2020. An Italian programme for COVID-19 infection in multiple sclerosis. Lancet Neurol. 19, 481–482.
Parrott, E, Kister, I, Charvet, L, et al., 2020. COVID-19 outcomes in MS: observational study of early experience from NYU Multiple Sclerosis comprehensive care center. Neurol. Neuroimmunol. Neuroinflamm. 7.
Montero-Escrubiano, P, Matias-Guiu, J, Gómez-Iglesias, P, Porta-Etessam, J, Pytel, V, Matias-Guiu, JA, 2020. Anti-CD20 and COVID-19 in multiple sclerosis and related disorders: a case series of 60 patients from Madrid, Spain. Mult. Scler. Relat. Disord. 42, 102185.
Berger, JR, Brandstätter, R, Bar-Or, A, 2020. COVID-19 and MS disease-modifying therapies. Neurol. Neuroimmunol. Neuroinflamm. 7 (4).
Stuve, O, Søodbøng Soerensen, P, Leist, T, et al., 2019. Effects of cladribine tablets on lymphocyte subsets in patients with multiple sclerosis: an extended analysis of surface markers. Ther. Adv. Neurol. Disord. 12, 1–16.
Cook, S, Verniersch, P, Comi, G, et al., 2011. Safety and tolerability of cladribine tablets in multiple sclerosis: The CLARITY (CLAdriBine tablets treating multiple sclerosis orally) study. Mult. Scler. J. 17, 578–593.
Minotti, C, Torelli, F, Barbieri, E, Giaquinto, C, Donà, D, 2020. How is immunosuppressive status affecting children and adults in SARS-CoV-2 infection? A systematic review. J. Infect. 81, e61–e66.
Giovannoni, G, Hawkes, C, Lechner-Scott, J, Levy, M, Wabnent, E, Gold, J, 2020. The COVID-19 pandemic and the use of MS disease-modifying therapies. Mult. Scler. Relat. Disord. 39, 102073.
Buonomo, A, Brescia Morra, V, Zappulo, E, et al., 2020. COVID-19 prevention and multiple sclerosis management: The SAFE pathway for the post-peak. Mult. Scler. Relat. Disord. 44, 102282.
Lisboa Bastos, M, Tavares, G, Abidi, SK, et al., 2020. Diagnostic accuracy of serological tests for COVID-19: systematic review and meta-analysis. BMJ 370, m2516.

Marcello De Angelis, Maria Petracca, Roberta Lanzirollo, Vincenzo Brescia Morra, Marcello Moccia* Multiple Sclerosis Clinical Care and Research Centre, Department of Neuroscience, Reproductive Science and Odontostomatolgy, Federico II University of Naples, Via Sergio Pansini 5, 80131 Naples, Italy. E-mail address: marcello.moccia@unina.it (M. Moccia).

* Corresponding author.