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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Correspondence

Favorable outcomes after COVID-19 infection in multiple sclerosis patients treated with cladribine tablets

Dear Editor,

The COVID-19 pandemic has caused unprecedented disruption to normal social and economic life worldwide. As of the end of June 2020, over 10 million cases have occurred worldwide with approximately 500,000 deaths (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). The disease is caused by a novel zoonotic coronavirus, SARS-CoV-2, which infects cells via the angiotensin-converting enzyme receptor type 2 expressed on cells of the respiratory tract and also key tissues such as the brain. (Butowt and Bilinska, 2020; Wölfel et al., 2020).

Two observations of the proposed pathogenic mechanisms of COVID-19 may be relevant to the treatment of patients with multiple sclerosis (MS). The coronaviruses responsible for the previous SARS and MERS outbreaks were shown to suppress natural interferon (IFN) responses. Evidence from patients with the most severe forms of COVID-19 also show profound downregulation of IFN-stimulated gene expression. (Park and Iwasaki, 2020) In addition, lymphopenia is very commonly observed in patients with COVID-19. (Guan et al., 2020; Huang et al., 2020) Severe lymphopenia has been associated with poorer outcomes compared to patients with higher lymphocyte counts at admission. (Onder et al., 2020; Zhou et al., 2020).

These observations are relevant because recombinant IFN beta has been approved for the treatment of relapsing forms of MS for over 20 years, (Jakimovski et al., 2018) and many, more recently approved agents reduce either absolute lymphocyte count (ALC) or certain subsets of lymphocytes. (Reich et al., 2018) Recent data provide some reassurance regarding the severity of COVID-19 in patients with MS, whether treated with a disease-modifying drug or not (Louapre et al., 2020; Sormani, 2020). However, more data are needed.

Here we report on the cases of COVID-19 occurring in MS patients treated with cladribine tablets (Mavenclad®) within the Merck KGaA Global Patient Safety Database. While such voluntary pharmacovigilance data might be incomplete, (Hughes et al., 2020) they can provide an additional level of detail on individual drugs to the information emerging from the national and international registries for COVID-19 occurring in patients with MS. (Louapre et al., 2020; Sormani, 2020).

As of 29 June, approximately 19,000 patients with relapsing MS have been treated with cladribine tablets. On this date, there were 46 patients with confirmed or suspected COVID-19 within the safety database. Patient age was available for 35 patients, with a range of 22–67 years. There were 26 females, 12 males, and 8 patients for whom gender was not reported. Cases were defined as confirmed if a confirmatory diagnostic test was reported as positive. If no confirmatory test was performed or reported, then cases were described as suspected. Due to the well-documented issues with false negative rates with polymerase chain reaction (PCR) testing techniques for COVID-19, (Woloshin et al., 2020) suspected cases that conformed to the World Health Organization diagnostic criteria were included in our analysis even if a negative PCR test was reported. Cases were designated as serious if they fulfilled the criteria of hospitalized, considered to be life-threatening, or medically significant. In keeping with usual pharmacovigilance practices, outcome was classified as recovered, recovering, not recovered, fatal, or not reported.

Of the 46 total cases, 18 cases were confirmed (Fig. 1). In 3 cases, confirmation included a report of a positive immunoglobulin G test at a time after COVID-19 symptom onset. Four of the confirmed cases were classified as serious (as hospitalization was required in 3 cases and the physician reported 1 case classified as “medically significant”). Among the suspected COVID-19 cases 2 were classified as serious (1 due to hospitalization and 1 which the physician classified as “medically significant”).

The majority of patients with suspected or confirmed COVID-19 had mild to moderate respiratory symptoms. Two confirmed cases had not reported experiencing any COVID-19 symptoms. None of the cases (either suspected or confirmed) received mechanical ventilation and there were no deaths. There was no indication for relevant involvement of other organ systems, in particular no ischemic complications were reported.

Cladribine tablets are taken during short dosing periods at the beginning of Years 1 and 2 of treatment. Each dosing period consists of 2 treatment weeks (of up to 5 days) separated by 1 month. The ALC nadir occurs in months 2–3 after the start of each treatment year, with counts increasing gradually thereafter for the rest of year. The median ALC in the first year remains above the lower limit of normal (LLN). In the second year median ALC remains above 800 cells/mL and recovers to above the LLN before the end of the treatment year. (Giovannoni et al., 2010) The time to onset of COVID-19 from last dose of cladribine tablets was available for 21/46 patients, with a median of 180 days (i.e. approximately 6 months after the last dose; range 3–559 days). Two patients experienced COVID-19 onset between the treatment weeks of Year 1 or Year 2, with the second treatment week delayed until symptoms resolved. Another patient who experienced COVID-19 onset shortly before commencing Year 2 also had treatment delayed until symptoms resolved.

In keeping with the use of immunosuppressive drugs in other conditions during the COVID-19 pandemic, (Russell et al., 2020) our data do not suggest that patients with MS treated with cladribine tablets and who acquire COVID-19 are at more risk of a severe outcome. We look forward to further data being reported from the MS registries.

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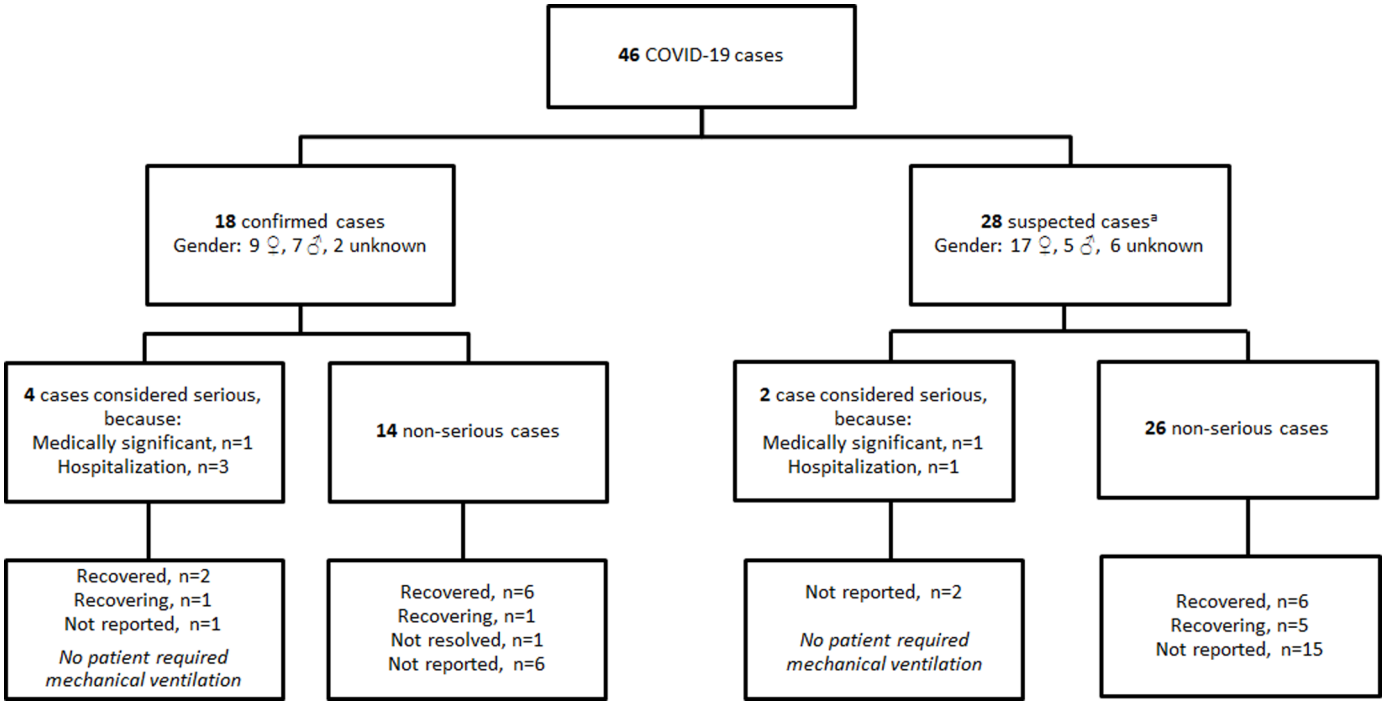

Fig. 1. Overview of COVID-19 infections and outcomes in patients treated with cladribine tablets.
[a]Includes 7 patients with negative PCR test.

Declaration of Competing Interest

DJ and AN are employees of Merck KGaA, Darmstadt, Germany. AG is an employee of Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany.

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References

Butowt, R., Bilinska, K., 2020. SARS-CoV-2: olfaction, brain infection, and the urgent need for clinical samples allowing earlier virus detection. ACS Chem. Neurosci. 11, 1200–1203.
Giovannoni, G., et al., 2010. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N. Engl. J. Med. 362, 416–426.
Guan, W., et al., 2020. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 382, 1708–1720.
Huang, C., et al., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497–506.
Hughes, R., et al., 2020. COVID-19 in persons with multiple sclerosis treated with ocrelizumab – a pharmacovigilance case series. Mult. Scler. Relat. Disord. 42, 102192.
Jakimovski, D., et al., 2018. Interferon β for multiple sclerosis. Cold Spring Harb. Perspect. Med. 8, a032003.
Louapre, C., et al., 2020. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2020.2581. online ahead of print.
Onder, G., et al., 2020. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 323, 1775–1776.
Park, A., Iwasaki, A., 2020. Type I and type III interferons – induction, signaling, evasion, and application to combat COVID-19. Cell Host Microbe. 27, 870–878.
Reich, D.S., et al., 2018. Multiple sclerosis. N. Engl. J. Med. 378, 169–180.
Russell, B., et al., 2020. Associations between immune-suppressive and stimulating drugs and novel COVID-19 - a systematic review of current evidence. Ecancermedicalscience 14, 1022.
Sormani, M.P., 2020. An Italian programme for COVID-19 infection in multiple sclerosis. Lancet Neurol. 19, 481–482.
Wölfel, R., et al., 2020. Virological assessment of hospitalized patients with COVID-2019. Nature 581, 465–469.
Woloshin, S., et al., 2020. False negative tests for SARS-CoV-2 infection - challenges and implications. N. Engl. J. Med. 383, e38 Epub ahead of print.
Zhou, F., et al., 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395, 1054–1062.

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