Journal of Neurology (2021) 268:2697–2699
https://doi.org/10.1007/s00415-020-10309-4

LETTER TO THE EDITORS

COVID-19 in cladribine-treated relapsing-remitting multiple sclerosis patients: a monocentric experience

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Received: 27 August 2020 / Revised: 2 November 2020 / Accepted: 8 November 2020 / Published online: 20 November 2020

Dear Sirs,

Cladribine is a purine nucleoside analog that inhibits DNA synthesis and repair in highly dividing cells inducing B- and T-cell apoptosis [1]. Through a selective but transient depletion of these lymphocyte subsets [1, 5], cladribine significantly reduces disease activity and disability progression in relapsing–remitting multiple sclerosis (RRMS) patients [2–4].

The SARS-CoV-2 pandemic has raised several concerns regarding the use of immunosuppressants in RRMS patients [6], since they are vulnerable to infections due to their disability and the use of drugs acting specifically on the immune system [7].

However, the influence of cladribine on the risk of developing COVID-19 disease is still unclear. Only two case series with three RRMS patients reported no or mild COVID-19 disease [8] or moderate pneumonia [9].

Here, we evaluated the prevalence and clinical features of COVID-19 disease among RRMS patients treated with cladribine in our center in Lombardy, Italy. From the whole MS population of our center, those treated with cladribine (Table 1) were asked if they had developed manifestations suggestive of COVID-19 disease up to August 25th 2020. Detailed demographic, clinical, and laboratoristic characteristics were collected.

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Case report

Since the pandemic start, 2/56 (3.6%) RRMS treated with cladribine complained a symptomatology suggestive of COVID-19 disease.

The first RRMS patient is a 30-year-old male, with a short disease duration (1.4 years), mild disability (Expanded Disability Status Scale [EDSS] score = 1.5), and no comorbidities (Table 2). He started cladribine on January 10th 2020. One week later, he developed fever (< 37.5°), ageusia, cough, fatigue, sputum production, sore throat, nasal congestion, shortness of breath without desaturation, and conjunctivitis. Serology for SARS-CoV-2 was negative in May 2020. Blood examinations performed before and after COVID-19 disease were within normal limits, except for a mild lymphopenia (0.9*10^9/liter) after cladribine administration.

The second RRMS patient is a 40-year-old female with a disease duration of 13.4 years, moderate disability (EDSS = 3.5), and no comorbidities (Table 2). She started cladribine on February 13th 2020 and underwent the second week of the first treatment course from March 5th 2020. On March 30th, she developed fever (< 37.8°), anosmia, ageusia, cough, fatigue, and bone/joint pain. Serology for SARS-CoV-2 performed in May 2020 was positive. Blood examinations both before and after COVID-19 disease were normal.

Both patients stayed at home, were telephone-monitored by their neurologists, and fully recovered within 2 weeks. Unfortunately, both patients did not perform nasal swabs during the symptomatic phase of COVID-19 disease.

Discussion

In line with recent reports [8–11], only a minority of RRMS patients receiving cladribine (2/56, 3.6%) developed a mild and self-limiting COVID-19 disease. This prevalence was similar to that of the whole MS population of our center

Table 1 Main demographic and clinical characteristics of RRMS patients treated with cladribine in our center

Variable	Cladribine-treated RRMS patients in our center ($n=56$)
Male/female (%)	17 (30%)/39 (70%)
Mean age (SD) [years]	33.8 (8.1)
Median disease duration (IQR) [years]	5.2 (2.1–11.1)
Median EDSS (IQR)	1.5 (1.0–2.0)
Median treatment duration* (IQR) [months]	15.8 (12.9–20.5)

*at the last available follow-up (August 25th 2020)

EDSS Expanded Disability Status Scale; *IQR* interquartile range; *RRMS* relapsing–remitting multiple sclerosis; *SD* standard deviation

(84/2950, 2.8%). Of note, at August 25th 2020, nasal/pharyngeal swabs have been found positive in 0.98% of the Lombardy population.

Although cladribine treatment is associated with peripheral lymphocyte depletion [5], our findings are consistent with data from randomized-controlled trials [12], showing that infections with cladribine are infrequent and, typically, self-limiting.

It is noteworthy that, in our cohort, COVID-19 disease occurred only in two RRMS patients close to treatment course and the possible nadir of selective immunosuppression. Accordingly, cladribine treatment could be safe during the COVID-19 pandemic. However, some precautions are needed during the first weeks after cladribine administration, when the risk of SARS-COV-2 infection could be higher due to transient immunosuppression. Further studies are necessary to evaluate whether cladribine could also prevent the cytokine storm associated with the most severe manifestations of COVID-19 disease [13].

In conclusion, young RRMS patients treated with cladribine, without comorbidities and with transitory systemic immunosuppression, are likely to show a risk of COVID-19 infection and complications that are similar to the general population.

Table 2 Main demographic, clinical, and laboratoristic findings of RRMS patients treated with cladribine and developing COVID-19 disease

Variable	Case #1		Case #2	
Sex	Male		Female	
Age [years]	30.5		40.0	
Disease duration [years]	1.4		13.4	
EDSS	1.5		3.5	
Comorbidities	No		No	
Treatment duration [months]	At COVID-19 onset	At the last FU (Aug 25th 2020)	At COVID-19 onset	At the last FU (Aug 25th 2020)
	0.2	7.6	1.5	6.8
Blood exams	Before COVID-19 (Dec 21st 2019)	After COVID-19 (Jan 31st 2020)	Before COVID-19 (Mar 3rd 2020)	After COVID-19 (Apr 20th 2020)
Leukocytes (*10^9/L)	6.27	7.80	10.10	8.40
Neutrophils (*10^9/L)	2.81	5.90	7.10	5.00
Lymphocytes (*10^9/L)	1.96	0.90	2.10	1.80
CD3 + (%)	N.A	65.8%	N.A	N.A
CD3 + /CD4 + (%)	N.A	42.8%	N.A	N.A
CD3 + /CD8 + (%)	N.A	20.5%	N.A	N.A
CD20 + (%)	N.A	11.4%	N.A	N.A

EDSS Expanded Disability Status Scale; *FU* follow-up; *L* liter; *N.A.* not available; *RRMS* relapsing–remitting multiple sclerosis

Author contributions PP: study concept, data gathering, drafting, and revising the manuscript. MAR: study concept, data gathering, drafting, and revising the manuscript. AN: data gathering and revising the manuscript. LM: data gathering and revising the manuscript. MF: study concept, data gathering, drafting, and revising the manuscript.

Funding No targeted funding reported.

Compliance with ethical standards

Conflicts of interest P. Preziosa received speakers honoraria from Biogen Idec, Novartis, Merck-Serono, and ExceMED. M.A. Rocca received speakers honoraria from Biogen Idec, Novartis, Genzyme, Teva, MS, R, Celgene, and Bayer, and receives research support from the MS Society of Canada and Fondazione Italiana Sclerosi Multipla. A. Nozzolillo has nothing to disclose. L. Moiola has received honoraria from Companies Biogen, Roche, TEVA, Sanofi, Serono, and Novartis. MF is Editor-in-Chief of the Journal of Neurology; received compensation for consulting services and/or speaking activities from Bayer, Biogen Idec, Merck-Serono, Novartis, Roche, Sanofi Genzyme, Takeda, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

Ethics approval This study has been approved by the local ethics committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate All patients provided consent to be anonymously included in this report.

Consent for publication All authors have consented to publication.

Availability of data and material Not applicable.

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