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Potential COVID-19 infection in patients with severe multiple sclerosis treated with alemtuzumab

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ABSTRACT

Background: Management of disease-modifying therapies in Multiple Sclerosis (MS) during the COVID-19 pandemic is a controversial issue. Alemtuzumab is an immunosuppressive drug that induces lymphocytes depletion. In this study, we aimed to evaluate the frequency and severity of COVID-19 in a case series of patients treated with alemtuzumab in our center.

Methods: Ten patients with a diagnosis of relapsing-remitting MS were phoned and asked about symptoms suggestive and COVID-19 using a semi-structured questionnaire.

Results: The mean age was 43.7 ± 9.65 years old, and 8 (80%) were females. The mean time since disease diagnosis was 17.30 ± 8.59 years, and all were patients with relapsing-remitting MS. Mean time from the last dose of Alemtuzumab was 9.80 ± 6.64 months, and last lymphocyte count was 760 ± 231 / μL. Two patients (20%) developed symptoms highly suggestive of COVID-19. Disease duration was 2 and 7 days. None patient required hospital admission. Patients with COVID-19 symptoms had longer clinical course of MS. Conversely, we did not find statistically significant differences regarding age, EDSS, last lymphocyte count, and months since the last dose of alemtuzumab administered between patients having or not symptoms of COVID-19.

Conclusions: Our data suggest that patients receiving alemtuzumab showed very mild symptoms of COVID-19. We speculate that immune reconstitution induced by treatment may induce positive changes in the immune system in the defense against SARS-CoV2. Further research about alemtuzumab and their role in COVID-infection is necessary to confirm these preliminary findings.

1. Introduction

Since the onset of the COVID-19 pandemic, the management of disease-modifying therapies is a controversial issue in patients with MS and other autoimmune disorders. In theory, and using the information available from other viral infections, patients under immunosuppressive drugs could be more susceptible to the COVID-19 infection or have a worse outcome. Thus, first recommendations suggested the temporary delay of some of these therapies, especially those associated with lymphocytes depletion, such as rituximab, ocrelizumab, or alemtuzumab (Brownlee et al., 2020; Coles et al., 2020; Giovannoni et al., 2020; Novi et al., 2020; Quinti et al., 2020).

However, preliminary observations in MS, and specifically in patients receiving anti-CD20 rituximab and ocrelizumab, suggests a low severity of the infection (Giovannoni, 2020; Montero-Escribano et al., 2020; Sormani et al., 2020). To date there is limited data about alemtuzumab and COVID-19 infection (Sormani et al., 2020). Alemtuzumab is a humanized IgG1 antibody targeting the glycophosphatidylinositol-anchored CD52 protein expressed in lymphocytes (Li et al., 2018). It induces depletion of cells expressing CD52 through antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and pro-apoptotic pathways. Consequently, alemtuzumab causes a profound B- and T-cell depletion (Cohen et al., 2012; Coles et al., 2012; Hartung et al., 2015). Alemtuzumab is currently used in patients with severe Multiple Sclerosis (MS), and some transplants (Bhowmick et al., 2016). Because patients with Alemtuzumab are also those with more severe forms of the disease, higher susceptibility to COVID-19 effects could even be more hazardous.

In this study, we aimed to evaluate the frequency and severity of COVID-19 in a case series of patients treated with alemtuzumab in our center.

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2. Methods

This is a single-center observational case series study evaluating the frequency and severity of COVID-19 among patients with MS (Thompson et al., 2018) followed up in the Department of Neurology of a tertiary hospital in Madrid, Spain. All patients were contacted by phone from 5th to 8th May 2020 (Matias-Guiu et al., 2020), when confirmed cases in the Region of Madrid accounted for 64,333. Because of the Government's decision of testing with RT-PCR only in patients requiring hospital admission, cases with suggestive symptoms were also considered. The hospital's Ethics Committee approved the research protocol (reference 20/242-E), and patients gave oral informed consent.

Demographic and clinical characteristics about MS were obtained from the last regular consultation during December 2019-February 2020. The neurologist responsible for the care of each patient since at least five years contacted by phone with each patient. A semi-structured interview was conducted using a questionnaire including: relapses during the pandemic, clinical characteristics of these relapses, pseudo-relapses, and other symptoms associated to MS; symptoms suggestive of COVID-19, characteristics, duration, consequences (hospital admission), and RT-PCR performance. The same questions about COVID-19 were also asked to the people living with MS patients or close contacts directly to the relatives when possible, or through the patients with MS. Average duration of each interview was 20 min.

2.1. Statistical analysis

Statistical analysis was conducted using SPSS Statistics v20. Descriptive results are shown as mean ± standard deviation or median (interquartile range), and frequency (percentage). We used the Mann-Whitney U test to compare two groups (patients with and without COVID-19 symptoms). A p-value <0.05 was considered statistically significant.

3. Results

3.1. Description of cases

We included ten patients treated with alemtuzumab at the onset of the pandemic. The mean age was 43.7 ± 9.65 years old, and 8 (80%) were females. The mean time since disease diagnosis was 17.30 ± 8.59 years, and all were patients with relapsing-remitting MS. Mean time from the last dose of alemtuzumab was 9.80 ± 6.64 months, and last lymphocyte count was 760 ± 231 / μL.

Two patients (20%) developed symptoms highly suggestive of COVID-19. The first patient was a 54 years-old woman with an EDSS of 6.5 who presented fever and diarrhea for two days and had at least two relatives also affected. One of them was her husband, who presented fever, cough, fatigue, and pleuritic chest pain for three weeks at the same time. The second case was a 51 years-old female with EDSS 6.5 that developed fever, ageusia, anosmia, asthenia, headache, and diarrhea for one week. He had no relatives affected. No patient required hospital admission, and both cases were not assessed by RT-PCR. However, the first case had a positive serological study (IgG) one month later.

The main demographic and clinical characteristics are shown in Table 1. In addition, one case did not show any symptom despite her husband presented fever and cough for more than one week with RP-PCR positive for COVID-19.

3.2. Comparison between patients with and without COVID-19

We compared baseline characteristics of patients showing or not COVID-19 symptoms. We did not find statistically significant differences regarding age (52.50 ± 2.12 in COVID-19 vs. 41.50 ± 9.56 in non-COVID-19, $U = 2.0$, $p = 0.116$), sex (100% of females vs 75%, $X^2 = 0.625$, $p = 0.622$), EDSS ($U = 7.0$, $p = 0.785$), last lymphocyte count (750 ± 353 vs. 762 ± 226 $U = 7.5$, $p = 0.895$), and months since last dose administered (13 ± 0 vs 9.0 ± 7.28, $U = 3.0$, $p = 0.185$). Patients with COVID-19 symptoms had longer clinical course of MS (29.50 ± 9.19 vs. 17.30 ± 8.59, $U = 0.0$, $p = 0.034$)

4. Discussion

The use of immunosuppressive therapies in patients with autoimmune disorders is a major concern during the COVID-19 pandemic. In this regard, several authors recommend conservative approaches to minimize the risk of severe SARS-CoV2 infection in patients with MS (Giovannoni et al., 2020). However, the potential negative impact of immunosuppressive therapies in patients with MS and COVID-19 have been questioned according to the increasing knowledge of the pathophysiology of COVID-19 infection and the preliminary evidence in MS patients (Giovannoni et al., 2020).

One of the worrisome drugs in the setting of COVID-19 is alemtuzumab, which produces a profound depletion of circulating B- and T-cells after the administration. Lymphocytes repopulated in the following months, and B-cells usually recover completely within six months, while T-cells recover more slowly and do not return to baseline counts by 12 months after treatment administration. Our study found two patients probably infected by COVID-19 that had received the last dose one year before and showed mild and short symptoms of the disease. Furthermore, one case was not infected or did not show any symptoms despite living with a relative infected with RT-PCR confirmation. These findings, although very preliminary, may suggest that patients treated with alemtuzumab did not show a higher risk of COVID-19 infection or greater severity. Likewise, patients with MS and alemtuzumab seemed to show milder and shorter forms of COVID-19 in comparison to their relatives. Alemtuzumab produces a lymphocyte reconstitution of the immune system, with the development of a new generation of lymphocytes from a new lineage (Hartung et al., 2015), starting with regulatory T-cells, but with a relevant role of memory lymphocytes. Perhaps the lymphocyte reconstitution induced by alemtuzumab, including changes in composition, phenotype, and function of lymphocytes, may confer a potential resistance of this new lineage to the virus or avoiding the cytokine storm associated with life-threatening complications such as cardiac dysfunction, respiratory failure, and coagulopathy (Liu et al., 2020). Furthermore, immune changes induced by alemtuzumab, which has been compared with a "*reset*" of the immune system, might be compared with the case of children infected by SARS-Cov2 (Zhang et al., 2013). In children, the immune system and T-cells seem to be more efficient in the response against SARS-Cov2 with excellent outcomes (Dong et al., 2020). In addition, children are less prone to the raise of pro-inflammatory cytokines including IL-6 that leads to the development of cytokine storm and pulmonary inflammation (Wang et al., 2020). Interestingly, patients treated with alemtuzumab also show lower levels of IL-6 (Zhang et al., 2013). On the one hand, these findings suggest that alemtuzumab should be safe in the current context. The only baseline factor associated with the infection was the time since diagnosis, an aspect that would suggest that patients with longer MS might be more susceptible to the infection, although this issue should be replicated in other samples because all patients were not exposed to the same risk of contagion. On the other hand, although we have no evidence of patients recently treated and exposed to SARS-CoV2 infection, we may hypothesize about a potential role of alemtuzumab in the acute management of cytokine storm of COVID-19. In this regard, tocilizumab, an IL-6 inhibitor, is being tested for the treatment of severe COVID-19 with promising results (Alattar et al., 2020). However, the potentially affected individuals reported had demographics associated with recovery (Guan et al., 2020; Myers et al., 2020) and were infected when cells potentially involved in immunity against the SARS-CoV2 would have

Table 1
Main clinical and demographic characteristics.

Age (years)	Sex	Years of disease	Last dose of Alemtuzumab (month)	Number of treatment courses received	Last lymphocytes count /μL	Diagnosis of COVID-19 infection	Relatives living at home with Covid-19 infection
54	Female	36	February 2019	2	1000	Yes	Yes, two cases
51	Female	23	February 2019	2	500	Yes	No
63	Female	20	October 2019	2	900	No	No
44	Female	13	September 2019	1	800	No	No
43	Male	22	April 2019	2	700	No	No
41	Female	18	March 2018	3	900	No	No
37	Male	13	February 2020	2	300	No	No
37	Female	9	February 2019	1	600	No	No
34	Female	13	January 2020	2	1000	No	No
33	Female	6	October 2019	2	900	No	Yes, one case

recovered (Baker et al., 2020).

The confirmation in further studies that alemtuzumab poses no special risk after immune reconstitution may also be important if a vaccine is successfully developed. In this regard, some vaccines under evaluation are based on attenuated viruses, which may be hazard in immunosuppressed patients. However, most of the vaccines under development are based on other mechanisms (inactivated virus, viral vectors, recombinant proteins, etc.) (Thanh Le et al. 2020). Regarding the response to vaccination, it is not expected to be reduced according to the experience with other vaccines, although this issue should be further investigated specifically with SARS-Cov2 vaccines (McCarthy et al., 2013).

Our study has some limitations. First, our sample size is limited, and none patient recently treated with alemtuzumab was infected. Indeed, none of our patients received alemtuzumab during the pandemic, and those patients that developed COVID-19 showed partial or complete lymphocyte reconstitution in the last count. Larger and multicenter studies would be necessary to confirm these findings and to evaluate the safety of patients receiving alemtuzumab during the pandemic. The definition of the risk of COVID-19 in the different immunological phases after treatment with alemtuzumab may have important implications in the current situation to optimize the therapeutic management as well as the recommendations about quarantine and self-protection for patients with MS. Second, none MS patient was evaluated with RT-PCR. However, all patients had highly suggestive clinical symptoms of COVID-19 and several relatives affected in familial clusters as in most COVID-19 cases. In addition, the absence of RT-PCR may reinforce our results because patients had no laboratory confirmation of the infection due to mild symptoms not requiring hospital admission.

In conclusion, our study suggests that alemtuzumab seems to be safe in the context of the COVID-19 pandemic. Furthermore, we speculate whether alemtuzumab may even be a therapeutic option for the COVID-19 infection itself, given the mechanism of action generating a reconstituted immune system more resistant to the virus and reducing the risk of the cytokine storm. Further research is necessary to confirm our findings.

CRediT authorship contribution statement

Jorge Matías-Guiu: Conceptualization, Methodology, Data curation, Investigation, Writing - original draft. **Paloma Montero-Escribano:** Conceptualization, Data curation, Investigation. **Vanesa Pytel:** Formal analysis, Writing - review & editing. **Jesús Porta-Etessam:** Investigation, Writing - review & editing. **Jordi A. Matias-Guiu:** Formal analysis, Writing - original draft.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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