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Correspondence

Alemtuzumab in Covid era



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ABSTRACT

Background: The SARS-CoV-2 pandemic impact on people with Multiple Sclerosis (pwMS) continues to worry. The disease modifying therapies in pwMS can add a more severe risk of infection when compared to the general population. Alemtuzumab is an anti-CD52 monoclonal antibody and it is one of the most immunosuppressive drugs used in Multiple Sclerosis (MS).

Case Description: We present a case of Covid-19 infection that occurred in a 24-year-old woman with MS and treated with alemtuzumab. The infection occurred 4 months after administration of the first course of alemtuzumab and had a benign course with subsequent development of antibodies. Furthermore, we present a brief review of the literature on similar published cases.

Discussion: We reviewed 17 articles concerning COVID-19 infection in MS patients in treatment with Alemtuzumab. In our case and all screened cases no severe course of disease was noted and no fatality was observed. Systematic compilation of this observation comforts clinicians about the course of Covid-19 infection despite alemtuzumab immunosuppressive treatment

Conclusions: The risk of serious COVID-19 disease in MS patients treated with alemtuzumab is unknown. Physicians need to monitor carefully pwMS treated with alemtuzumab and to consider COVID-19 infection related relapse in the MS patients. Further research is recommended to evaluate the beneficial-risk profile of alemtuzumab in pandemic era.

1. Introduction

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is a new infectious disease (Zhou et al., 2020) and its sudden worldwide spread has developed urgent and global countermeasures in every medical science (Chandrashekar et al., 2020).

Since coronavirus disease 2019 (COVID-19) was declared as a pandemic disease in March 2020, people with multiple sclerosis (PwMS) were immediately recognized as a vulnerable population due to the required combination of immunosuppressive therapies. Given the high infection rates and incidence of SARS-CoV-2, practitioners were suddenly faced difficult questions about continuation or interruption of therapy. The prevalent concern has been if immunosuppression through DMT usage could increase the risk of infection. Although overall disease-modifying therapies appear relatively safe (Parrotta et al., 2020, Hughes et al., 2020), there may be concerns related to individual strategies based on recent data. For example, patients on B cell-depleting therapies, such as rituximab and ocrelizumab, may not be adept to develop protective IgM and IgG antibodies (Meca-Lallana and Aguirrea, 2020) and thus are at higher risk of infection. Case studies have demonstrated that patients in treatment with B-cell depleting recovered from SARS-CoV-2 infection, affirming that innate and/or acquired protective mechanisms against the virus remain effective (Novi et al., 2020). However, more recent worldwide data have indicated an increased risk of serious infections for patients on these therapies (Maria et al., 2021). Furthermore, a large European prospective cohort study (RADAR-CNS) identified a trend for increased risk of SARS-CoV-2 infection in patients

taking alemtuzumab or cladribine compared to injectable drugs independently of age, sex and disease course. However there is no evidence of worse covid-19 in these patients (Costa et al., 2020).

Here, we reported the case of COVID-19 occurring in a 24-years-old female MS patient, 4 months after the first alemtuzumab administration and a review of the literature on similar published case reports.

2. Material and methods

A review of the literature was performed in compliance with the PRISMA guidelines (Moher and Tetzlaff, 2009). Screening was performed by reviewing article titles or full text up to February 2021 using electronic the database Pubmed.

The review criteria were the search for case report on patients treated with alemtuzumab in multiple sclerosis and infected by SARS-CoV-2. The primary search terms included "Alemtuzumab AND Covid". Seventeen citations appeared. The extracted citations were then screened. Five articles met eligibility criteria for our qualitative review.

2.1. Case presentation

We reported a case of COVID-19 in a patient with MS previously treated with alemtuzumab, a humanized anti-CD52 monoclonal antibody.

A 24-year-old woman affected by relapsing-remitting MS with high disease activity for about 6 years. The patient at 5 years of age underwent heart valve repair and she takes ACE-inhibitors and beta-blockers.

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Over the years, the patient has shown clinical and radiological relapses of the disease so she received therapy with interferon, dimethyl fumarate, natalizumab and cladribine. Afterwards, in July 2020, due to severe clinical relapse, EDSS worsening to 3 and high radiological activity, she switched to alemtuzumab.

The administration of alemtuzumab was free of side effects or subsequent complications. After 4 months from the infusion of the first course of alemtuzumab, in November 2020 the patient underwent a nasopharyngeal swab for SARS-CoV-2 RNA research due to contact tracing following a family members positivity to COVID-19 infection.

At that time the patient had regular blood tests for alemtuzumab which showed only mild leukopenia and grade 3 lymphopenia ($0.4 \times 10^3 / \mu\text{L}$). The SARS-Cov-2 RNA test was positive. The patient had no fever, dyspnea, rash, diarrhea or other complications of COVID-19 disease being completely asymptomatic. Therefore, home quarantine was ordered and during this period, she complained for a few days mild asthenia and low-grade fever responsive to paracetamol.

She tested negative on two repetitive nasopharyngeal swabs in December 2020. In January 2021, she resulted positive for anti-SARS-CoV-2 IgG antibodies (Capasso et al., 2020).

3. Discussion

Clinical manifestations of COVID-19 infection typically include fever, cough, fatigue, and often lung involvement, but these symptoms appear to be mild in most patients. However, about 10% of patients may develop severe illness with respiratory failure that may require hospitalization and intensive care management (Guan et al., 2020). At the beginning of the COVID-19 pandemic, several postulates were formulated about immunosuppressed patients. Patients taking immunosuppressive therapies might be more susceptible to a more aggressive COVID-19 disease. On the other hand, it has been proposed that immunosuppression may not be a risk factor. The prevention of exaggerated immune response could mitigate clinical deterioration (Mehta et al., 2020).

In this report we described a case of a patient with MS and treated with alemtuzumab who contracted COVID-19 infection, with asymptomatic clinical course. In consideration of other previous reports, we hypothesized that immunosuppression does not play an unfavorable role in these patients. This hypothesis was supported since the patient contracted COVID-19 infection only 4 months after her first course of alemtuzumab and the blood-count showed lymphopenia grade 3 at the time of the infection [table 1].

Previous reports showed a benign course of covid 19 infection. They considered young patients (under fifty), affected by RRMS and without

comorbidities like our patient [table 2].

The patient is young with cardiac comorbidities and with low MS-related disability. She recovered without complications and developed IgG antibodies against SARS-CoV-2, even with extremely low lymphocyte counts. To the best of our knowledge, only seven other similar cases have been published [table 2]. These similar cases, with uncomplicated COVID-19 infection despite alemtuzumab-induced lymphopenia, have been described at different time: one week (Carandini et al., 2020, Fernández-Díaz and Gracia-Gil, 2020), two months (Guevara et al., 2020), three months (Fiorella and Lorna, 2020) and one year (Fiorella and Lorna, 2020, Fernández-Díaz and Gracia-Gil, 2020) after the alemtuzumab infusion.

Alemtuzumab is an anti-CD52 monoclonal antibody and is one of the most immunosuppressive drugs used in MS. It caused rapid and prolonged depletion of circulatory T and B lymphocytes (Baker et al., 2017). An increased risk of infections has been described during treatment with alemtuzumab, including viral respiratory infections among the most concerning complications (Syed, 2021).

Therefore, it is conceivable that alemtuzumab involves a theoretical increased risk of developing a severe form of COVID-19 infection, particularly if the infection occurs before immune reconstitution.

In general, it is believed that long-term T cell depletion could be a cause of acute infection and that B cell depletion may affect vaccine response and the development of antibodies providing long-term immunity (Tobias et al., 2019, Zheng and Kar, 2020).

Therefore, immunosuppression was considered a risk factor for COVID-19 infection. However, no concrete evidence until now supports or denies this claim. Most of treated PwMS infected by COVID-19 disease had a favourable clinical outcome (Hughes et al., 2020).

It is interesting to note that also with other immunosuppressive therapies only a small number of PwMS develop Covid-19 infection (Paolo et al., 2020). Data from our review are consistent with the actual knowledge about the mechanism of alemtuzumab. Some immunocompetence is maintained despite drug treatment: the depletion in the lymphoid organs is poor and the innate immune response is mostly preserved, since macrophages, NK cells and neutrophils have a low expression of CD52 (Wray et al., 2019).

Furthermore, an additional explanation could be that drug-induced immunosuppression would not allow the over-expression immune system avoiding an event known as a "cytokine storm" which is responsible for the most aggressive disease course (Hojyo et al., 2021) and potentially serious drug-related side effects (Iovino et al., 2019). Hence, immunosuppression is considered protective because severe acute respiratory syndrome (SARS) is related to a dysregulated immune response (Giovannoni et al., 2020). The production of IgG antibodies during immunosuppression allows us to hypothesize the efficacy of the vaccine for COVID-19 in these patients but will have to be verified if the immune response can be considered valid over time [table 2].

To date, no reports have reported complicated COVID-19 infections in PwMS treated with alemtuzumab. Interestingly, our analysis of pharmacovigilance data by European database of suspected adverse drug reaction reports showed only 14 cases of Covid-19 with alemtuzumab and no fatalities (28). However, the general recommendation is to postpone infusions of alemtuzumab until the pandemic is controlled (Giovannoni et al., 2020, Brownlee et al., 2020). In times of uncertainty, we should consider carefully treatment options to successfully manage MS. In some PwMS with highly active MS, the risk of a disabling relapse or disease progression may outweigh the risk of serious complications from SARS-CoV-2 infection (28).

The main risks for severe COVID, even in the MS population are the same as those for the general population (i.e. age, co-morbidities such as respiratory illness, smoking, obesity, hypertension, diabetes and being generally frail), none of which our patient had. Therefore her asymptomatic course would probably had been similar even in the absence of treatment with alemtuzumab. However, the risk of serious COVID-19 disease in MS patients treated with alemtuzumab is still unknown, but

Table 1
Personal and clinical characteristics of the patient.

	CASE
Baseline	
Age (years)/sex	24/female
comorbidities	heart valve repair
Multiple Sclerosis	
Type	RRMS
Current EDSS	3
Disease duration (years)	6
Previous DMT	Interferon, dimethyl fumarate, natalizumab, cladribine
Alemtuzumab 1° cycle	August 2020
Alemtuzumab 2° cycle	No
COVID-19	
Onset	November 2020
Diagnostic method	
Nasopharyngeal swab	Positive
lymphopenia	$0.4 \times 10^3 / \mu\text{L}$
Severe disease	No
Hospitalization	No
Treatment	Paracetamol
Serum IgG SARS-Cov-2	Positive (January 2021)

Table 2

Personal and clinical characteristics of previously reported covid patients treated with alemtuzumab.

	CASE (Guevara et al., 2020)	CASE (Matías-Guiu et al., 2020)	CASE (Matías-Guiu et al., 2020)	CASE (Carandini et al., 2020)	CASE (Mehta et al., 2020)	CASE (Fiorella and Lorna, 2020)	CASE (Fiorella and Lorna, 2020)
Baseline							
Age (years)/sex	24/female	43/male	30/female	35/male	25/female	54/female	51/female
comorbidities	depression	No	Ex-smoker	No	-	-	-
Multiple Sclerosis							
Type	RRMS*	RRMS	RRMS	RRMS	RRMS	RRMS	RRMS
Current EDSS	0	0	2.5	1	-	6.5	6.5
Disease duration (years)	-	14	2.5	2.0	-	36	23
Previous DMT	-	Fingolimod, Interferon	-	-	-	-	-
Alemtuzumab 1° cycle	April 2019	April 2018	March 2019	December 2018	February 2019	-	-
Alemtuzumab 2° cycle	February 2020	April 2019	March 2020	February 2020	February 2020	February 2019	February 2019
COVID-19							
Onset	May 2020	March 2020	March 2020	April 2020	February 2020	May 2020	May 2020
Diagnostic method							
Nasopharyngeal swab	positive	positive	positive	positive	positive	No	No
lymphopenia	$4,5 \times 10^3 / \mu\text{L}$	$0,2 \times 10^3 / \mu\text{L}$	$0,0 \times 10^3 / \mu\text{L}$	$0,7 \times 10^3 / \mu\text{L}$	$0,09 \times 10^3 / \mu\text{L}$	$1,0 \times 10^3 / \mu\text{L}$	$0,5 \times 10^3 / \mu\text{L}$
Severe disease	No	No	Bilateral pneumonia	No	No	No	No
Hospitalization	No	No	4 days	No	No	No	No
Treatment	Acetaminophen/levodropopizine	Amoxicillin, Lopinavir/ritonavir/Hydroxychloroquine	Hydroxychloroquine	No	Acetaminophen	-	-
Serum IgG SARS-Cov-2	Positive (January 2021)	Positive (May 2020)	Ceftriaxone/cefditoren Positive (May 2020)	-	-	Positive (June2020)	-

* RRMS: relapsing remitting multiple sclerosis:- unavailable

considering the cases reported in literature, alemtuzumab does not appear to be associated to a higher risk of severe COVID-19 infection. Evidently more research on alemtuzumab and its role in COVID-19 infection is needed to confirm these preliminary findings.

Declaration of Competing Interest

N.O. is employed by Sanofi.

The others 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.

Consent for publication

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Aniello Iovino^{a,b,*}, Nunzio Olivieri^c, Francesco Aruta^a, Emanuele Giaquinto^a, Lucia Ruggiero^a, Emanuele Spina^a, Stefano Tozza^a, Fiore Manganelli^a, Rosa Iodice^{a,b,c,d}
^a *Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, Naples, Italy*
^b *Department of Advanced Biomedical Sciences, University of Naples "Federico II", Via Pansini 5, 80131, Naples, Italy*
^c *Department of Biology, University of Naples "Federico II", Via Mezzocannone 8, 80134 Naples, Italy*
^d *IRCCS SDN, Naples Via Emanuele Gianturco, 11, 80143, Naples, Italy*

* Corresponding author.

E-mail address: anielloiovino@msn.com (A. Iovino).