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Case report

COVID-19 in 7 multiple sclerosis patients in treatment with ANTI-CD20 therapies

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A B S T R A C T

Background and aim: In December 2019, the first cases of SARS-CoV-2 infection were detected in Wuhan. Within two months, it had begun to spread around the world in what became an unprecedented pandemic. Patients with Multiple Sclerosis (MS) in a state of immunosuppression may be considered at risk for complications in the COVID-19 pandemic, although there is increasing evidence postulating a possible protective role of selective immunosuppression. One group of such immunosuppressants used in MS comprises the anti-CD20 monoclonal antibodies (mAbs) ocrelizumab and rituximab. Anti-CD20 mAbs bind to the surface of B cells, causing their depletion. We describe our experience in seven cases of patients with multiple sclerosis who have been affected by SARS-COV-2 (with a clinical/serological diagnosis or PCR diagnosis) and who were being treated with anti-CD20+ monoclonal antibodies.

Material and methods: We review the development of patients during infection as well as the resolution of their clinical picture. We also analyze the serology status against SARS-CoV-2 after resolution of the infection.

Results: Although the severity of the clinical pictures was variable, patients' development was good. Not all patients, however, developed antibodies against SARS-CoV-2.

Conclusions: Patients treated with anti-CD20+ have adequate resolution of COVID-19 despite the fact that the presence of antibodies against SARS-CoV-2 was not detected in all cases. It is possible that the presence of humoral immunity is not always necessary fora good clinical course of SARS-CoV-2 infection.

1. Introduction

In December 2019, the first cases of SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection were detected in Wuhan. This is the third coronavirus zoonosis to affect humans in 20 years and this time it has led to a rapidly spreading pandemic (Perlman, 2020). The COVID-19 (Coronavirus disease 2019) pandemic has forced neurologists to make quick and important decisions with MS patients using immunosuppressive treatment. Ocrelizumab and rituximab are anti-CD20 monoclonal antibody (mAb) treatments used in MS. Ocrelizumab is a humanized monoclonal antibody against CD20+ and an approved treatment for relapsing and progressive MS (RMS and PMS). Rituximab is a chimeric monoclonal antibody against CD20+, initially approved for CD20+ non-Hodgkin lymphoma and later for CD20+ chronic lymphocytic leukemia and rheumatoid arthritis and used in neuromyelitis optica as an off-label MS treatment. Both anti-CD20 mAbs bind to the surface of B cells, causing their depletion (Moreno Torres and García-Merino, 2017).

Here, we describe our experience with seven patients treated with these drugs who suffered from COVID-19. The main clinical characteristics and treatments of the cases detailed below are summarized in Table 1.

2. Case reports

Case 1: 60-year-old male, diagnosed with RMS in 2010, started on treatment with glatiramer acetate, switched to natalizumab in 2013. In 2017, treatment was changed to rituximab due to persistent radiological activity and clinical progression (he was diagnosed at that time as being secondary progressive). The patient had an Expanded Disability Status Scale (EDSS) value of 8. In December 2019, CD19+ cells were absent from the peripheral blood. The patient presented on March 17 due to a four-day course of fever, cough and dyspnea. The main laboratory findings were: lymphopenia ($0.60 \times 10^3/mm^3$), slight decrease in Ig M(Immunoglobulin M) M(58.6 mg/dl, range: 80 - 250), positive SARS-CoV-2 RT-PCR in nasopharyngeal swab. Chest x-ray showed infiltrates in left hemithorax. The patient showed good clinical and radiological evolution with specific SARS-CoV-2 treatment (hydroxychloroquine 200 mg/12 h for 10 days) and was discharged home five days after admission without sequelae and with a negative PCR

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Table 1
Clinical and phenotype characteristics of multiple sclerosis patients.

	AGE (YEARS)	MS PHENOTYPE	MS EVOLUTION TIME (YEARS)	EDSS	NO. OF PREVIOUS TREATMENTS	PREVIOUS TREATMENT	COMORBIDITIES	MS TREATMENT	TREATMENT TIME	LAST INFUSION
PATIENT 1	60	PMS	10	8	2	Natalizumab	no	Rituximab	3 years	July 2019
PATIENT 2	49	RRMS	6	3	1	Glatiramer Acetate	Smoker	Ocrelizumab	3 years	January 2019
PATIENT 3	45	RRMS	5	2	1	Teriflunomide	no	Ocrelizumab	3 years	January 2020
PATIENT 4	25	RRMS	8	1	3	Rituximab	no	Ocrelizumab	1 month	March 2020
PATIENT 5	36	RRMS	11	2	2	Rituximab	no	Ocrelizumab	7 months	September 2019
PATIENT 6	60	PPMS	16	7.5	0	NO	NO	Ocrelizumab	9 years	November 2019
PATIENT 7	52	PPMA	19	7.5	1	Glatiramer Acetate	NO	Ocrelizumab	16 months	October 2019

	CD19+ *T* lymphocytes	Previous lymphopenia	COVID-19 DATE	SARS-CoV-2 RT-PCR	Chest x-rays	COVID-19 Lymphopenia	OTHERS	HOSPITALIZATION	COVID-19 SEVERITY	COVID-19 TREATMENT	IMMUNIZATION
PATIENT 1	Absent, December 2019	no	17 March 2020	POSITIVE	Unilateral pneumonia	0.60 × 10^3/ mm^3	Fibrinogen: 489, D-DIMER: 0.54, LDH: 255, CRP: 9.3,	YES	SEVERE	Hydroxychloroquine 200 mg/ 12 h 10 days	NOT DETERMINED
PATIENT 2	Absent, January 2020	no	11 March 2020	POSITIVE	Normal	0.51 × 10^3/ mm^3		YES	MODERATE	lopinavir/ ritonavir 200/ 50 mg 2 tablets/ 12 h	IgM- IgG +
PATIENT 3	Absent, January 2020	no	3 April 2020	POSITIVE	Bilateral pneumonia	NO	CRP 0.83 mg/dl	YES	SEVERE	Hydroxychloroquine 200 mg/ 12 h 10 days, lopinavir/ ritonavir 200/ 50 mg 2 tablets/ 12 horas, Azithromycin 250 mg/24 h 4 days	IgG + IgM +
PATIENT 4	Absent, March 2020	no	April 2020	POSITIVE	NORMAL	NO	NO	NO	ASYMPTOMATIC	No	IgG- IgM-
PATIENT 5	Absent, December 2019	no	April 2020	UNKNOWN	UNKNOWN	UNKNOWN	UNKNOWN	NO	MILD	No	IgG- IgM-
PATIENT 6	UNKNOWN	no	March 2020	UNKNOWN	UNKNOWN	UNKNOWN	UNKNOWN	NO	MILD	NO	NOT DETERMINED
PATIENT 7	Absent October 2019	no	May 2020	POSITIVE	UNKNOWN	NO	UNKNOWN	NO	ASYMPTOMATIC	NO	IgG + IgM +

Abbreviations. CRP, C-reactive protein. EDSS, Expanded Disability Status Scale. LDH, lactate dehydrogenase. MS, multiple sclerosis. PP, progressive. RR, relapsing. RT-PCR, reverse transcription polymerase chain reaction.

swab in May 2020.

Case 2: 49-year-old male, smoker, diagnosed with RMS in 2014, started treatment with glatiramer acetate in 2015. Due to suboptimal response, switched to ocrelizumab in 2017. Last infusion was in January 2020, when CD19+ cells were absent from the peripheral blood. EDSS was 3. Attended emergency department on March 11 with a five-day history of cough, associated with dyspnea and fever. The main laboratory findings were lymphopenia (0.51×10^3 mm^3) and C-reactive protein (CRP) 4.95 mg/dL. Chest x-ray findings were normal and he tested positive for SARS-CoV-2 RT-PCR in nasopharyngeal swab. Specific SARS-CoV-2 treatment was started (lopinavir/ritonavir 200/50 mg 2 tablets/12 h) and he was discharged on the fifth day of admission because of good clinical evolution. Control RT-PCR for SARS-CoV-2 in nasopharyngeal swab on April 22 was negative. Serology showed positive IgG and negative IgM.

Case 3: 45-year-old male, diagnosed with RMS in 2015, started treatment with teriflunomide, replaced by ocrelizumab in March 2017 due to lack of efficacy. Last infusion was in January 2020, when CD19+ cells were absent from the peripheral blood. He showed no lymphopenia, mild hypogammaglobulinemia (IgG: 696 mg/dl, range: 800 – 1600; IgM: 48.7 mg/dl, range: 80 – 250; normal IgA) and EDSS 2. The patient attended emergency department on April 3 due to a ten-day history of cough, dyspnea, myalgia and low-grade fever. Laboratory data showed slight increase in CRP (0.83 mg/dl). He presented a chest x-ray with bilateral infiltrates and positive SARS-CoV-2 RT-PCR in nasopharyngeal swab. SARS-CoV-2 treatment was started (hydroxychloroquine 200 mg/12 h for 10 days, lopinavir/ritonavir 200/50 mg 2 tablets/12 h, azithromycin 250 mg/24 h for 4 days), and the patient presented a very favorable evolution and was discharged after four days. The patient deteriorated five days after discharge, with dyspnea required readmission for monitoring for one week, although no further treatment was required. He was discharged without sequelae. Serology testing conducted on May 20 was positive for both IgG and IgM. PCR in nasopharyngeal swab was negative.

Case 4: 25-year-old female diagnosed with RMS in 2012 started on treatment with natalizumab, discontinued due to poor tolerability. From 2014 to 2018 she was on treatment with fingolimod, replaced by rituximab in December 2018 because of persistent radiological activity. Treatment was switched to ocrelizumab in March 2020 (first dose of 300 mg on March 4, 2020). EDSS value was 1. On April 15, prior to the scheduled administration of the second dose of ocrelizumab, she presented a positive SARS-CoV-2 RT-PCR in nasopharyngeal swab (performed as screening prior to immunosuppressive treatment). Blood count and Igs were normal and CD19+ cells were absent from the peripheral blood. Treatment was postponed. Control RT-PCR on April 22 was negative. Complete COVID-19 serology (IgG + IgM) was also negative. Seven days later, ELISA serology for IgG and IgM showed negative results. The patient has remained asymptomatic throughout this time and the second ocrelizumab infusion (300 mg) was performed in May 2020 without incident following two negative PCR tests.

Case 5: 36-year-old woman diagnosed with RMS, with a first spinal cord relapse in 2009. The patient began treatment with glatiramer acetate. It was decided to change treatment due to inefficacy as she had two relapses. She was started on treatment with rituximab in March 2019 because ocrelizumab had not yet been approved, and switched to ocrelizumab in September 2019 when it became available for her. Her EDSS was 2 and her clinical course was good, with no new relapses. Laboratory tests in December 2019 showed CD19+ cell depletion with no other changes. On April 1, she presented symptoms of fever and headache, reporting contact with a relative who died of COVID-19 the week before. There was no PCR confirmation. The patient recovered completely in one week without sequelae. Serology testing for IgG and IgM against SARS-COV-2 in May 2020 was negative.

Case 6: 60-year-old female first presented with a picture of progressive paraparesis and ataxia in 2004. After a complete examination, including cranial and spinal MRI, she was diagnoses with PMS. The patient accumulated disability over the years until starting treatment with ocrelizumab as part of a clinical trial in 2011. The patient maintained an impressive slow progression (from an EDSS of 6.5 to 7.5 in nine years with good upper limb function). On March 12, 2020, she presented a three-day picture of fatigue, headache, cough, 38 °C fever and hyposmia that subsided spontaneously and without treatment. Not confirmed by PCR or serology.

Case 7: 52-year-old male diagnosed with RMS in 2009. Treated with glatiramer acetate at the time he was diagnoses since he presented with a relapse. The patient presented progression after the first relapse, leading to a clinical impression of a 'SAP' (Single Attack with later Progression) form of MS. The patient was administered ocrelizumab treatment beginning in February 2019 due to MRI activity and continued progression. Serology (IgG and IgM) and PCR for SARS-CoV-2 were performed before administering his treatment dose in May 2020. Both were positive, and the patient was asymptomatic.

3. Discussion

Anti-CD20+ monoclonal antibodies are used in MS treatment. The incidence of severe infections from ocrelizumab in clinical trials was very low (1.3% for relapsing MS and 6.2% for primary progressive MS) (Hauser et al., 2017). Ocrelizumab is associated with decreased levels of IgM (and to a lesser degree for IgA and IgG), and serious infections occurred, but their incidence was low in clinical trials and extended phases (Derfuss et al., 2020). Clinical trials reported similar incidence of infections between rituximab and placebo (69.6% and 68.2% vs 65.3% and 71.4% respectively) (Moreno Torres and García-Merino, 2017). The incidence of infections in open-label prospective studies varies widely, ranging from 61.5% to 8%, however infections are generally mild to moderate (Midaglia et al., 2018). Rituximab decreases immunoglobulins, especially IgM levels, without a clear association with serious infection risk (Moreno Torres and García-Merino, 2017).

In this work, we report our experience in MS patients with anti-CD20+ antibodies who have presented SARS-CoV-2 infection. Even with differing clinical pictures, all presented favorable evolution, for which there are several hypotheses:

1 Patients treated with anti-CD20 may be capable of having a primary immune response in the initial phase of infection. Ocrelizumab and rituximab induce depletion of circulating CD20+ cells and not the B cells in secondary lymphoid organs, favoring an adequate immune response against primary infection (G Novi et al., 2020; Baker et al., 2018).
2 B cells and immunoglobulin may not be absolutely necessary for viral elimination. Perhaps in some especially milder cases, innate immunity anti-viral T cells may be sufficient for recovery (Wang et al., 2020; Soresina et al., 2020).
3 Several publications have suggested that selective immunosuppression prior to SARS-CoV-2 infection could benefit and even protect patients from its hyperinflammation phase, which is accompanied by a release of proinflammatory cytokines that can ultimately be fatal. It is hypothesized that the decrease in IL-6 releasing peripheral B cells could confer this protection to patients in the hyperinflammation phase (Giovanni Novi et al., 2020; Giovanoni, 2020).

In our series, all patients presented a favorable evolution, but it is worth mentioning patients 1, 6 and 7, who were older and had a higher EDSS. Worse infection evolution might therefore have been expected, yet they present adequate resolution of the clinical picture. Patients 6 and 7 in particular present a very mild clinical picture and an asymptomatic picture respectively. It should also be noted that patients 4 and 7 were asymptomatic carriers. Serology testing could not detect immune response to the virus in patients 4 and 5, but it did in patients 2, 3 and 7. This does not seem to be associated either with severity of the

picture presented or with being an asymptomatic carrier, as patient 7 for example did not present a clinical picture and developed antibodies. The absence of CD19 + *B* cells cannot fully explain this either, since this occurs in all the patients we have reported on. This could be explained by the fact that patients with negative serology (4 and 5) came off rituximab treatment before ocrelizumab and perhaps the use of both therapies was detrimental to antibody formation. In the VELOCE study, humoral responses were attenuated in patients who were B-cell depleted having received ocrelizumab. Patients were nonetheless able to have humoral responses to the vaccines and cellular immune responses were not assessed (Stokmaier et al., 2018). Adding in the use of rituximab, it is possible that this humoral response is reduced. Another option to consider is the possibility of false negatives in the test results.

As mentioned previously, COVID-19 resolution may not always necessarily require B cells. It is theorized that innate immunity or T-cell-mediated immunity might be sufficient in some patients to resolve the picture (Wang et al., 2020) because of the favorable evolution of infection in patients without B lymphocytes, as in X-linked agammaglobulinemia (Soresina et al., 2020).

4. Conclusion

Our experience with the evolution of patients treated with anti-CD20 drugs has been positive. We can hypothesize a 'protective' role of selective immunosuppression in the COVID-19 hyperinflammation phase, in addition to the preserved ability of patients treated with anti-CD20 to make an adequate primary immune response. This may help us make decisions in treatment doses in the current pandemic (Giovanoni, 2020). We have found antibodies against SARS-CoV-2 in patients treated with ocrelizumab, but in patients who previously used rituximab this immunity is not achieved or we are not able to detect it. Regardless of the presence or absence of antibodies, progression has been favorable in all cases and so resolution of the condition could be considered to be independent of humoral immunity. Greater experience through patient records is required in order to draw firm conclusions.

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