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Correspondence



Development of SARS-CoV-2 IgM and IgG antibodies in a relapsing multiple sclerosis patient on ofatumumab

A B S T R A C T

We report the case of a MS patient on subcutaneous ofatumumab who became infected with SARS-CoV-2 and remained asymptomatic while developing antiviral IgM and IgG antibodies. The patient was B-cell depleted with normal serum immunoglobulin levels. Anti-SARS-CoV-2 IgG antibodies remained positive three months after the initial infection. These findings suggest that a MS patient treated with ofatumumab may be able to mount an effective humoral response to SARS-CoV-2 infection and probably to COVID-19 vaccines as well. Further research will be necessary to evaluate the humoral response of MS patients on ofatumumab to SARS-CoV-2 infection and COVID-19 vaccines.

1. Introduction

The current COVID-19 global pandemic has raised important questions regarding the immune response to viral infection of MS patients treated with immunomodulating drugs, particularly those on highly effective anti-CD20 monoclonal antibodies like ocrelizumab and ofatumumab (Berger et al., 2020). Another point of great interest is how effectively patients treated with these drugs would respond to anti-SARS-CoV-2 vaccination.

We report a patient with relapsing MS (RMS) on subcutaneous ofatumumab therapy for 42 months who had laboratory-confirmed SARS-CoV-2 infection and developed antiviral IgM and IgG antibodies.

2. Case report

A 51-year-old woman diagnosed with MS in 2005 on ofatumumab 20 mg subcutaneously every four weeks since January 2017. She was enrolled into the phase 3 ASCLEPIOS-I (Hauser et al., 2020) trial and transitioned to the open-label extension study (ALITHIOS, 2018) until present.

The patient had contact with a family member who tested positive for COVID-19 infection, which prompted her to get tested. Pharyngeal swab testing for the SARS-CoV-2 viral RNA by PCR and serological testing were performed. Viral RNA was identified from the pharyngeal swab, and SARS-CoV-2 antibodies (IgM and IgG) to the viral spike protein were detected using the COVID-19 IgG/IgM Rapid Test Cassette, Whole Blood/Serum/Plasma, Healgen® (EUA Authorized Serology Test performance, 2021). The patient remained asymptomatic. Her ofatumumab injection was held until she tested negative on repeat COVID-19 swab testing two weeks after her initial positive test. The patient resumed ofatumumab injections and continued asymptomatic. Serological testing was repeated three months after the first antibody test. Anti-SARS-CoV-2 IgG to the spike protein was reported positive (Quest Laboratories, using the VITROS Anti-SARS-CoV-2 Total Reagent Pack and Calibrator, Ortho-Clinical Diagnostics, Inc.) (EUA Authorized Serology Test performance, 2021).

She had been fully B-cell depleted in blood, and her serum IgG and

IgM levels remained within normal limits (Table 1).

3. Discussion

Ofatumumab is a fully human anti-CD20 monoclonal antibody that selectively depletes B cells. It was recently approved by the FDA for the treatment of RMS. In phase 3 clinical trials, ofatumumab administered subcutaneously was highly effective to reduce clinical and MRI disease activity in RMS patients (Hauser et al., 2020; Milo, 2020). Serial serum IgM and IgG analysis from ASCLEPIOS I/II participants showed that IgG levels were decreased from baseline until week 36 and recovered up to baseline level at week 72 in ofatumumab treated patients. IgM levels were reduced from baseline but remained within the reference range for most of the patients in the ofatumumab group (De Seze et al., 2020).

Our MS patient was treated with ofatumumab for 42 months and was fully B-cell depleted with normal serum IgG and IgM levels when infected with the SARS-CoV-2 virus. She remained clinically asymptomatic. She mounted a successful humoral response to the virus with IgM and IgG antibodies, and anti-SARS-CoV-2 IgG remained positive three months after her initial positive serological testing.

The humoral response to selected vaccines of RMS patients treated with IV ocrelizumab, another anti-CD20 monoclonal antibody, was evaluated in a phase 3b trial (VELOCE) (Bar-Or et al., 2020). This study showed that patients receiving ocrelizumab mounted a diminished humoral response to these vaccines compared with the control group (no treatment or IFN- β). It was recently reported that two ocrelizumab-treated MS patients experienced symptomatic COVID-19 infection but did not develop SARS-CoV-2 antibodies several weeks post-infection (Thornton and Harel, 2020). Another MS patient on ocrelizumab with mild COVID-19 and mildly decreased IgG level developed anti-SARS-CoV-2 IgA several weeks after infection but no specific IgG response (Lucchini et al., 2020). Additionally, another patient on ocrelizumab with low IgG and IgM levels was SARS-CoV-2 IgG negative two months after COVID-19 infection. These findings have raised the concern of an attenuated humoral response in ocrelizumab-treated patients with hypogammaglobulinemia (Conte, 2020).

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Table 1

Serial blood CD19+B-cell count and serum IgM and IgG levels in a RMS patient treated with subcutaneous ofatumumab.

Date	CD-19 cells (%)	IgG mg/dL	IgM mg/dL
Dec 2019	0	1070	57
Feb 2020	0.2	1150	62
Jun 2020	0	1310	64

Reference range

CD-19 cells (5.0- 22 %)

IgG (565- 1765 mg/ dL)

IgM (40- 230 mg/ dL)

The findings from our patient suggest the possibility that patients on subcutaneous ofatumumab may be able to mount an effective humoral response to SARS-CoV-2 infection and probably COVID-19 vaccines. To date, there have been no published reports of patients on ofatumumab developing anti-SARS-CoV-2 antibodies. The humoral response of ofatumumab-treated patients to COVID-19 infection or vaccination is an important area that warrants further investigation.

Declaration of Competing Interest

R.E.F-G. declares no conflict of interest. J.H. received honoraria for consulting services from Novartis, Biogen, Banner Life Sciences, and Alexion. L.T. received honoraria from Biogen. K.R. received honoraria for consulting services from Novartis, Biogen, EMD Serono, Genzyme, TG Therapeutics. S.D. received honoraria for consulting services from Novartis.

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