Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Is serological response to SARS-CoV-2 preserved in MS patients on ocrelizumab treatment? A case report

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SUMMARY

The emergency represented by the COVID-19 pandemic represents a new challenge for clinicians who deal with autoimmune diseases because of patients undergoing immunosuppressive therapy. Few cases of Multiple Sclerosis (MS) patients receiving ocrelizumab who contracted COVID-19 with a benign course have recently been published.

We present the case of a MS patient with mild COVID-19 who developed SARS-CoV-2 specific IgA without IgG ten weeks after infection. Patients on B-cell depleting drugs have a reduced antibody immune response to viral neoantigens. A relative sparing of mucosal-associated lymphoid tissues (MALT) could be responsible for IgA response in our patient.

1. Main text

SARS-CoV-2 is a newly identified coronavirus responsible for Coronavirus disease 2019 (COVID-19). The pathology affects the respiratory system causing interstitial pneumonia. COVID-19 is mild in most affected patients but can be severe or even fatal in a significant proportion (near 15% in hospitalized patients) (Odone et al., 2020). The emergency represented by the COVID-19 pandemic represents a new challenge for clinicians who deal with autoimmune diseases since patients undergoing immunosuppressive therapy could have an increased risk of a severe course of infection. Few case reports of multiple sclerosis (MS) patients receiving ocrelizumab who contracted COVID-19 with a benign course have recently been published (Novi et al., 2020; Suwanwongse and Shabarek, 2020). Moreover, pharmacovigilance case series on cases of COVID-19 in the course of ocrelizumab has also been published (Hughes et al., 2020). In these studies, patients were assessed using a nasal and pharyngeal swab for SARS-CoV-2 but no serological study was performed nor reported.

We report the serological data of a patient with relapsing MS who developed COVID-19 in a mild form.

2. Case presentation

We present the case of sixty-year-old woman with an 8-year history of relapsing MS on ocrelizumab treatment who developed mild COVID-19.

At MS onset, the patient had lower limbs hypoesthesia and sphincter dysfunction with both brain and spinal cord lesions on MRI and oligoclonal bands on CSF examination. First treatment with glatiramer acetate was suspended after one year due to disease activity and replaced with Fingolimod. After 5 years, fingolimod was withdrawn following lymphopenia and the patient experienced clinical and radiological activity during wash-out. The patient was then given dimethyl fumarate for 6 months suspended for a new relapse with two new spinal cord lesions. Therefore, on April 2019 treatment with ocrelizumab was started and on October 2019 she underwent the most recent administration (2 completed treatment cycles). While on Ocrelizumab there were no clinical and radiological signs of disease activity. Last EDSS score was 2.5 and a brain and spinal MRI performed on March 2020 was stable.

Forty days before COVID-19 onset, the patient performed routine blood tests including cell blood count (CBC), lymphocyte subtypes, immunoglobulin dosage and liver and kidney function showing CD19+ complete depletion (normal CD4+ and CD8+) and IgG at lower limit (700 mg/dl, normal range 700–1600).

At the beginning of March 2020, the patient developed fever (maximum temperature 38 °C), productive cough, sore throat and nasal congestion. Patient started antibiotic treatment with levofloxacin 750 mg/day orally for 7 days and prednisone 25 mg/day orally for 15 days. She did not present any further worsening and did not require hospitalization or respiratory support. Symptoms gradually resolved after 2 weeks.

Fifteen days after symptoms' resolution, the patient underwent nasopharyngeal swab that resulted positive for SARS-CoV-2. A chest CT scan was performed with evidence of bilateral ground glass opacity and interstitial abnormalities. CBC, C-reactive protein, D-dimer, fibrinogen and liver and kidney function were normal. A nasopharyngeal swab repeated twice in the next two weeks was negative in both cases.

Ten weeks after the onset of COVID-19 symptoms (33 weeks after the last ocrelizumab infusion), the patient underwent blood examination with evidence of minimal B cells repopulation (CD19+ 4 cells/mm3; CD19/CD20 0.1%; CD19/CD27 + 0.0%) and slight IgG reduction (685 mg/dl, normal range 700–1600). A new nasopharyngeal swab was negative and SARS-CoV-2 serological test (ELISA; Euroimmun®, catalog: EI 2606–9601 A and G; CE registered and FDA approved) demonstrated the presence of IgA (4.5 S/CO; >1.1 positive) while IgG were absent (0.4 S/CO < 0.8; >1.1 positive).

3. Discussion

Ocrelizumab is a humanized anti-CD20 B cell–depleting antibody approved for treatment of MS. Anti-CD20 directed treatments generate

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an impairment of humoral immune response. Both ocrelizumab and rituximab (chimeric monoclonal anti-CD20 antibody) reduce antibody immune responses to neoantigens of viral origin (Nguyen et al., 2017; Stokmaier et al., 2018). Those drugs also reduce immunoglobulin levels, with IgG to a greater extent than IgM and IgA. Despite an optimal recovery from COVID-19, our patient did not develop a full serological response against SARS-CoV-2 as demonstrated by the absence of specific IgG production. It should be underlined that at present it is unclear if these antibodies are truly protective against SARS-CoV-2 reinfection (Lin et al., 2020).

Nevertheless, we found high level of IgA that are the most abundant immunoglobulin in mucosal tissues. IgA are produced in a compartmentalized lymphoid system, called mucosal-associated lymphoid tissues (MALT) (Boyaka, 2017). The dichotomy between IgG and IgA production in our patient may be explained by a lower effect of ocrelizumab on MALT relatively sparing IgA response (He et al., 2015).

Further prospective studies are needed to evaluate not only the severity of COVID-19 but also the consequent immunological response particularly in immunosuppressed patients. In COVID-19, some data show that 10–20% of symptomatically infected people have undetectable or low titre antibodies. It has been proposed that in some COVID-19 patients, low virus-binding antibody titres might correlate with more severe infections, or with having had a mild infection with little antigenic stimulation (Altmann et al., 2020). Although manufacturer reports for both IgG and IgA 95% sensitivity and higher than 99% specificity more than 10 days after infection, several papers that used the same ELISA test showed lower values highlighting a difference between IgA and IgG. IgG sensitivity is around 90% (86–91%) with specificity ranging between 96 and 98% while the IgA dosage appears less sensitive (near 83%) and specific (86–88%) (Beavis et al., 2020; Krüttgen et al., 2020; Montesinos et al., 2020). Therefore, we cannot completely rule out a false positive result for IgA in our patient.

We can expect a reduced humoral response in patients on B-cell depleting agents with a reduced proportion of patients developing IgG against SARS-CoV2. By contrast we cannot undervalue the important role of T-cells in the immunity response or to exclude a protective IgA response considering the transmission route of SARS-CoV-2.

Declaration of Competing Interest

Matteo Lucchini received: travel grants from Roche, Biogen, Novartis, Almirall and Sanofi-Genzyme; speaking and/or consulting fees from Biogen, Novartis, Merck-Serono and Almirall.

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Massimiliano Mirabella: scientific advisory board membership of Bayer Schering, Biogen, Sanofi-Genzyme, Merck, Novartis, Teva; consulting and/or speaking fees, research support or travel grants from Almirall, Bayer Schering, Biogen, CSL Behring, Sanofi-Genzyme, Merck, Novartis, Teva, Roche, Ultragenix; principal investigator in clinical trials for Biogen, Merck, Novartis, Roche, Sanofi Genzyme, Teva, Ultragenix.

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Matteo Lucchini[a,b,*,1], Assunta Bianco[a,b], Paola Del Giacomo[a], Chiara De Fino[a], Viviana Nociti[a,b], Massimiliano Mirabella[a,b]
[a] *Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Largo Agostino Gemelli 8, 00168 Rome, Italy*
[b] *Università Cattolica del Sacro Cuore, Rome, Italy*
E-mail address: lucchinimatteo87@gmail.com (M. Lucchini).

[*] Corresponding author.
[1] Orcid ID 0000-0002-0447-2297