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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 can 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) after 2 weeks.

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; Euroimmum®, 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 large neoantigens. A relative sparing of mucosal-associated lymphoid tissues (MALT) could be responsible for IgA response in our patient.
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.

Assunta Bianco received: travel grants and/or consulting fees from Roche, Biogen, Novartis and Sanofi-Genzyme.

Viviana Nociti: honoraria for speaking, advisory board, consulting from Teva, Sanofi-Genzyme, Almirall, Biogen, Bayer Schering, Merck, Novartis.

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, Ulnagenix; principal investigator in clinical trials for Biogen, Merck, Novartis, Roche, Sanofi Genzyme, Teva, Ulnagenix.

Paola Del Giacomo and Chiara De Fino have nothing to disclose.

Funding

None.

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