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Beyond COVID-19: DO MS/NMO-SD patients treated with anti-CD20 therapies develop SARS-CoV2 antibodies?

ABSTRACT

Since 2019, a new coronavirus infection (COVID-19) due to an agent called SARS-CoV-2 spread rapidly worldwide. Patients with multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMO-SD) are often treated with immunosuppressants. Beyond their effect on the risk of COVID-19 infection, the consequences on the long-term immune response against the coronavirus remain unknown. Among 13 MS or NMO-SD patients with confirmed COVID-19 included, all 5 patients treated with anti-CD20 therapies had a negative SARS-CoV-2 serology.

To date, maximal precautions to prevent coronavirus infection should be maintained in MS/NMO-SD patients already exposed to COVID-19 during anti-CD20 therapy.

1. Introduction

Since its emergence in Wuhan, China in December 2019, a new coronavirus infection (COVID-19) due to a agent called SARS-CoV-2 spread rapidly worldwide, reaching more than more than 25 000 000 people as of August 30, 2020.

Most patients with multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMO-SD) are treated with disease modifying therapies (DMTs) either immunomodulators or immunosuppressants. DMTs target different types of immune cells, impacting differently cellular and/or humoral immunity. MS experts have proposed a stratification of the risk of acquiring severe COVID-19 infection (Giovannoni et al., 2020), according to the immunodepletion related to DMTs.

However, beyond the effect of DMTs on the risk of COVID-19 infection, their potential effect on the long-term immune response against the coronavirus remains unknown. In this respect, compared to other DMTs, anti-CD20 therapies can impact immune response to infection or to vaccine due to their direct action on B cells (Hua et al., 2014). Three MS patients (Lucchini et al., 2020) (Thornton and Harel, 2020) were recently reported with negative SARS-CoV-2 antibody testing following COVID-19 infection.

We report the results of the SARS-CoV-2 serologic status of 13 MS and NMO-SD patients infected with COVID-19, which highlight that all patients on anti-CD20 therapies were seronegative.

2. Cases

Patients were included in the French registry of COVID-19 in patients with MS or NMO-SD (NCT04355611, approval from the ethic committee of Sorbonne University #CER-2020–19). The collection of non-opposition to the use of medical data was carried out according to French law, good clinical practice and GDPR.

We report SARS-CoV-2 serology for the first thirteen consecutive patients from Pitié-Salpêtrière Hospital, in Paris (Table 1): 7 female and 6 male, with median neurological disease duration of 17 years (range: 9–31). Twelve patients were on DMTs at the time of COVID-19 infection. Of the 5 patients on anti-CD20 therapy, one had a negative SARS-CoV-2 PCR, and one was not tested. Both patients were contact to people (wife or friend) diagnosed COVID-19 few days before, with positive SARS-CoV-2 PCR.

The median delay between COVID-19 symptoms onset and SARS-CoV-2 serology was 59 days (range: 23–76). SARS-CoV-2 serology was negative for the 5 patients treated by anti-CD20 antibodies. The median delay between the last administration of anti-CD20 therapy and the serology was 124 days (range: 69–180). In patients on anti-CD20 therapies, no hypogammaglobulinemia or lymphopenia was reported concomitantly in 3 patients, one patient had a grade 2 lymphopenia (740/mm3), and one patient had a severe grade 3 lymphopenia (370/mm3). When available (2/5), CD19 B-cells rate was low (0.03; 0.05%). Four patients were retested one month later: the SARS-CoV2 serology was still negative. For the 8 patients not treated by anti-CD20 DMTs, SARS-CoV-2 serology was positive. For the 7 patients with Abbott serology, the median IgG index was 7.97 (range: 2.19 - 9.77).

3. Discussion

We reported SARS-CoV-2 serology performed more than 3 weeks after COVID-19 infection in 13 patients with MS or NMO-SD. The serology was negative for all patients treated with monoclonal anti-CD20 antibodies.

CD20 is expressed at the surface of B-cells, from pre-B-cells stage to mature B-lymphocytes. B-cell depletion affects antibody production. In the HERMES study in MS (Hauser et al., 2008), treatment with rituximab (RTX) was associated with rapid and near-complete depletion of CD19+ peripheral B-lymphocytes from 2 weeks after treatment until

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| Patient | Diagnosis | Age (years) | Sex | Duration on current DMT (months) | Duration between last anti-CD20 administration and symptom onset (days) | COVID-19 diagnosis SARS-Cov2PCR | SARS-Cov2 serology (IgG index) | SARS-Cov2 serology technique | Duration between COVID-19 clinical onset and SARS-Cov2 serology (IgG index) (days) | Anti-CD20 DMTs |
|---------|-----------|-------------|-----|-------------------------------|---------------------------------------------------------------|-----------------------------|--------------------------------|--------------------------------|--------------------------------------------------------------------------------|----------------|
| 1       | NMO-SD    | 20          | F   | 10                            | 31                                                            | Positive                     | Negative                        | Abbott                         | 59                                                                 | Ofatumumab 3 |
| 2       | PPMS      | 49          | M   | 6                             | 13                                                            | Positive                     | Negative                        | Abbott                         | 46                                                                 | Rituximab 7 |
| 3       | SPMS      | 55          | M   | 6                             | 36                                                            | Positive                     | Negative                        | Abbott                         | 132                                                                | Rituximab 3 |
| 4       | RRMS      | 34          | F   | 5.5                           | 118                                                           | Positive                     | Negative                        | Roche                          | 59                                                                 | Ocrelizumab 5 |
| 5       | RRMS      | 39          | F   | 1                             | –                                                             | Fever                        | Negative                        | Abbott                         | 59                                                                 | None |
| 6       | RRMS      | 49          | M   | 8                             | 144                                                           | Pneumonia, ground glass opacities on thoracic CT scan, hospitalized with supplemental oxygen | Positive                        | Abbott                         | 66                                                                 | Teriflunomide 6 |
| 7       | RRMS      | 38          | M   | 2                             | –                                                             | Anosmia, ageusia, fever, cough | –                              | Abbott                         | 40                                                                 | Glatiramer 4 |
| 8       | SPMS      | 27          | F   | 2                             | –                                                             | Anosmia, ageusia, fever, cough | –                              | Abbott                         | 54                                                                 | Glatiramer 7 |
| 9       | RRMS      | 41          | M   | 3                            | 35                                                            | Pneumonia, ground glass opacities on thoracic CT scan, hospitalized with supplemental oxygen | Positive                        | Abbott                         | 132                                                                | Dimethylfumarate 6 |
| 10      | RRMS      | 34          | F   | 1                             | –                                                             | Fever                        | Positive                        | Biosynex                       | 59                                                                 | None |
| 11      | RRMS      | 49          | M   | 8                             | 144                                                           | Pneumonia, ground glass opacities on thoracic CT scan, hospitalized with supplemental oxygen | Positive                        | Abbott                         | 68                                                                 | Natalizumab 144 |
| 12      | RRMS      | 30          | F   | 0                             | –                                                             | Anosmia, ageusia, fever, cough | –                              | Abbott                         | 76                                                                 | Natalizumab 34 |
| 13      | RRMS      | 49          | M   | 4                            | 72                                                            | Pneumonia, ground glass opacities on thoracic CT scan, hospitalized with supplemental oxygen | Positive                        | Abbott                         | 71                                                                 | Dimethylfumarate 72 |

Abbreviations: NMO-SD: neuromyelitis optica spectrum disorder; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; DMT: disease modifying therapy; M: male; F: female.

* The patient's spouse had a diagnosis of COVID-19 confirmed by positive SARS-CoV-2 PCR.
* The patient reported a contact 3 days before symptoms onset with a friend who was confirmed of COVID-19 diagnosis by positive SARS-CoV-2 PCR.
24 weeks.

Several studies on vaccination (influenza, H1N1, pneumococcal vaccine) in patients with rheumatoid arthritis treated with RTX have been reported (Hua et al., 2014; Kapetanovic et al., 2014; Westra et al., 2014). IgM and IgG secretion was significantly decreased compared to patients treated with other immunosuppressant or healthy controls. It suggests that anti-CD20 therapy impairs the humoral response after these vaccines.

In a large cohort study of 285 patients with COVID-19 infection, all patients seroconverted between 17 and 19 days after symptom onset (Long et al., 2020). In our case series, all patients had a SARS-CoV-2 serology, at least 23 days after symptoms onset. However, to date, in the general population, the immunogenicity against SARS-CoV-2 and the potential duration of this immunity are unknown. Moreover the potential for cross-reactivity with other coronaviruses (yielding false-positives) have to be determined (Kirkcaldy et al., 2020).

The interpretation of SARS-CoV-2 serologies must be careful in patients with immunosuppressive therapies. The strategy regarding DMTs management in MS or NMO-SD might be hampered by the difficulties to retrospectively confirm COVID-19 especially on patients with anti-CD20 as in our cohort. Even if IgG index is very heterogeneous in the general population, it is striking that none of the 5 patients on anti-CD20 had a positive serology. If larger studies confirm that patients on anti-CD20 have a reduced or absent humoral response to COVID-19 infection, this could suggest that these patients may be more vulnerable to a re-infection, although data are lacking to conclude if presence of such antibodies might confer protection against re-infection. It is still unclear if impaired humoral response to SARS-CoV-2 due to anti-CD20 therapies might be responsible for more severe clinical forms of COVID-19 in the acute phase. First steps of immune response to SARS-CoV-2 mainly imply the innate immune system, including macrophages, innate lymphoid cells, followed by antiviral T cell response, while acute adaptive B cell response occurs later during the infection and is involved in virus clearance (Vabret et al., 2020). If a vaccine against SARS-CoV-2 becomes available in the future, vaccination strategy will also be challenging for patients on anti-CD20 who previously developed COVID-19. To date, in the absence of long-term longitudinal studies, maximal precautions to prevent coronavirus infection, including social distancing and barrier measures, should be maintained even in MS/NMOSD patients who have already presented COVID-19 infection.

CRediT authorship contribution statement

Elisabeth Maillard: Conceptualization, Data curation, Formal analysis, Writing - original draft. Caroline Papeix: Formal analysis, Writing - review & editing. Catherine Lubetzki: Conceptualization, Writing - review & editing. Thomas Roux: Formal analysis, Writing - review & editing. Valérie Pourcher: Formal analysis, Writing - review & editing. Céline Louapre: Formal analysis, Supervision, Writing - review & editing.

Declaration of Competing Interest

Dr. Maillard reports personal fees from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, Teva and grants from Novartis and Roche, outside the submitted work.

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