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

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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 NMOSD 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/NMOSD 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 here 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/mm^3), and one patient had a severe grade 3 lymphopenia (370/mm^3). 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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Table 1
Description of the cohort of MS/NMO-SD patients.

	Age (years)	Sex (M/F)	Diagnosis	EDSS	Current DMT	Duration on current DMT (months)	Duration between last anti-CD20 administration and symptom onset (days)	COVID-19 diagnosis	SARS-Cov2 PCR	SARS-Cov2 serology (IgG index)	SARS-CoV2 serology technique	Duration between COVID-19 clinical onset and SARS-COV2 serology (days)
Anti-CD20 DMTs												
1	20	F	NMO-SD, AQP4+	3	ofatumumab	31	**10**	Anosmia, asthenia	Positive	Negative	Abbott	59
2	49	M	PPMS	6	rituximab	13	**59**	Pneumonia, ground glass opacities on thoracic CT scan, hospitalized with supplemental oxygen	Positive	Negative	Abbott	46
3	41	M	SPMS	7	rituximab	30	**132**	Anosmia, ageusia, fever, cough	Not done*	Negative	Biosynex	23
4	55	M	PPMS	3	rituximab	36	**59**	Pneumonia, ground glass opacities on thoracic CT scan, hospitalized with supplemental oxygen	Negative**	Negative	Roche	65
5	34	F	RRMS	5.5	ocrelizumab	35	**118**	Pericarditis, pneumonia, ground glass opacities on thoracic CT scan, hospitalized with supplemental oxygen	Positive	Negative	Roche	64
DMTs other than anti-CD20												
6	49	F	RRMS	2	teriflunomide	53	–	Anosmia, ageusia, fever, cough, dyspnea	Not done	Positive (9,77)	Abbott	66
7	38	M	RRMS	2	glatiramer	4	–	Anosmia, ageusia, fever, dyspnea	Not done	Positive (7,97)	Abbott	51
8	27	F	SPMS	2	glatiramer	7	–	Anosmia, ageusia, fever, cough	Not done	Positive (4,86)	Abbott	54
9	41	M	RRMS	3	dimethyl-fumarate	66	–	Anosmia, ageusia, fever, cough, dyspnea	Not done	Positive (8,42)	Abbott	40
10	39	F	RRMS	1	none	–	–	Fever	Positive	Positive	Biosynex	32
11	56	F	RRMS	8	natalizumab	144	–	Pneumonia, ground glass opacities on thoracic CT scan, hospitalized with supplemental oxygen	Positive	Positive (8,52)	Abbott	68
12	30	F	RRMS	0	natalizumab	34	–	Anosmia, ageusia, fever, cough	Not done	Positive (2,19)	Abbott	76
13	49	M	RRMS	4	dimethyl-fumarate	72		Pneumonia, ground glass opacities on thoracic CT scan, hospitalized with supplemental oxygen	Positive	Positive (6,8)	Abbott	71

Abbott serology by chemiluminescent microparticulate immunoassays (index IgG positive: ≥1.4).
Roche serology by electrochemiluminescence (ECLIA) on the Cobas® system (Roche Diagnostics, Bâle, Suisse) (index IgG positive : ≥1.0).
Biosynex serology by immunochromatography (quick serologic test without IgG index quantification).
Abbreviations: NMO-SD: neuromyelitis optica - spectrum disorders; AQP4: aquaporine 4; 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-Cov2 PCR.

** COVID-19 diagnosis was confirmed on thoracic CT showing bilateral ground glass opacities. He reported a contact 3 days before symptoms onset with a friend who was confirmed of COVID-19 diagnosis by positive Sars-Cov2 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 Maillart: 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. Maillart reports personal fees from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, Teva and grants from Novartis and Roche, outside the submitted work.

Dr. Papeix reports personal fees from Biogen, Medday, Merck, Novartis, Roche, Sanofi-Genzyme, Teva, outside the submitted work.

Pr. Lubetzki reports grants and personal fees from BIOGEN, personal fees from MERCK-SERONO, personal fees from ROCHE, personal fees from REWIND, personal fees from IPSEN, outside the submitted work.

Dr. Roux reports personal fees from Biogen, Merck, Teva, outside the submitted work.

Pr Pourcher reports personal fees from Biogen, Merck, Novartis, Roche, outside the submitted work.

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