Post-vaccine COVID-19 in patients with multiple sclerosis or neuromyelitis optica

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Abstract

Introduction: Recent studies suggested that anti-CD20 and fingolimod may be associated with lower anti-spike protein-based immunoglobulin-G response following COVID-19 vaccination. We evaluated if COVID-19 occurred despite vaccination among patients with multiple sclerosis (MS) and neuromyelitis optica (NMO), using the COVISEP registry.

Case series: We report 18 cases of COVID-19 after two doses of BNT162b2-vaccination, 13 of which treated with anti-CD20 and four with fingolimod. COVID-19 severity was mild.

Discussion: These results reinforce the recommendation for a third COVID-19 vaccine dose among anti-CD20 treated patients, and stress the need for a prospective clinical and biological study on COVID-19 vaccine efficacy among MS and NMO patients.

Introduction

Anti-CD20 (ocrelizumab; rituximab) are immunosuppressive therapies that profoundly deplete B lymphocytes. They are widely used to treat multiple sclerosis (MS) and Neuromyelitis Optica Spectrum Disorders (NMOSD) and have proven to be highly effective in reducing relapse rate and disability accumulation(1), with an increased risk of severe infections over time. During the recent Sars-CoV-2 pandemic, ocrelizumab and rituximab have been associated with a higher risk of severe COVID-19 (Odds Ratio 2.05[95% Confidence Interval 1.39;3.02])(2). Moreover, ocrelizumab exposure is also known to attenuate humoral responses to pneumococcal, influenzae, and tetanus toxoid vaccines(3), raising suspicion that B cell depletion may also impair vaccine efficacy. In a recent Israelian cohort study, only 22.7% (10 of 44) and 3.8% (1 of 26) of MS patients treated by anti-CD20 and Fingolimod respectively developed anti-spike protein-based positive serology following 2 doses of BNT162b2 vaccine(4).

The first COVID-19 vaccine (BNT162b2) was approved in France and Europe on December 21, 2020. On February 11, 2021, MS patients treated with anti-CD20 therapies became a priority population for vaccination. Later on, vaccination was recommended for all MS patients older than 50 years on March 2, 2021, and for all adult MS patients on May 12, 2021, although most patients could have access to vaccination in early April 2021.

As anti-CD20 therapies exposure is associated with COVID-19 severity and with lower anti-spike humoral immunity after vaccination, we aimed to assess if COVID-19 had occurred among previously vaccinated patients, and determine the characteristics of these patients.

Case series:

We used the COVISEP registry, the French database of COVID-19 in patients with MS or NMOSD, comprising 1650 MS and 67 NMOSD COVID-19 infected patients, on July 30, 2021. We extracted all cases of COVID-19 occurring since December 21, 2020, corresponding to 460 cases.

Sixteen MS patients were infected with Covid-19 more than 7 days after receiving their first dose of COVID-19 vaccine, and before receiving the second dose. Of them, 6 patients were treated with anti-CD20, 3 with natalizumab, 1 with fingolimod, teriflunomide, glatiramer, cladribine and dimethyl-fumarate and 2 had no treatment.

Eighteen patients were diagnosed with COVID-19 while they had received two doses of BNT162b2 vaccine, 17 had MS and 1 had aquaporine-4 positive NMOSD. The characteristics of these patients are summarized in Table 1. Median age (P25;P75) of post-vaccine COVID-19 patients was 36.8 (31.0;44.4) years, 14 (77.8%) were women, and only one had a comorbidity (Patient 13 had diabetes). All patients were diagnosed due to typical COVID-19 symptoms occurrence. COVID-19 first symptoms occurred at a median (P25;P75) of 21 (9;60) days after the second dose. Thirteen of the 18 patients (72.2%) were treated with anti-CD20 therapies, with a median (P25;P75) of 5 (4;6) cycles. Only one had low concentration of IgG (Patient 16: IgG 5.4 g/L). In contrast, among non-vaccinated COVID-19 patients in the COVISEP registry, 20.0% were treated with anti-CD20. Anti-CD20 exposure was associated with post-vaccine COVID-19 occurrence among MS and NMOSD patients (OR 10.4; CI [3.7;29.3], p<0.001). One patient (patient 18), treated with ocrelizumab, had previously been infected with Covid-19 thirteen months before, with laboratory evidence of anti-S COVID-19 immunity. Four of the 17 MS post-vaccine patients (23.5%) were treated with fingolimod, while the were 11.5% among MS non-vaccinated COVID-19 (OR for post-vaccine COVID-19 occurrence in MS patients treated with fingolimod: 2.3; CI [0.75;7.1], p=0.146). Only one patient was treated with another disease modifying therapy (DMT) (patient 17: interferon beta), and none among non-treated patients. In three patients without prior infection, COVID-19 first symptoms began within 7 days after the second dose. Covid-19 severity was generally mild, but one patient (patient 1) required intensive care hospitalization, without the need for mechanical ventilation.

Discussion:

In the COVISEP registry, 18 patients have been infected with COVID-19 after 2 doses of BNT162b2 vaccine, 13 of them were treated with anti-CD20 therapies, and four with fingolimod, indicating that COVID-19 occurrence after a double vaccine dose was not uncommon among these patients. By comparison, in the BNT162b2 randomized trial, including exclusively non-immunocompromised patients, with a median follow up of two months, 9 patients on 18556 were infected after two doses. In contrast, only one case of post-vaccine COVID-19 occurred among patients treated with other DMTs and none among untreated patients. In France in June 2021, among the 59301 MS treated patients, 6185 MS patients were treated with Ocrelizumab (10.4% of MS treated patient)(5). The number of patients treated with Rituximab in France was not available, but these patients represented one third of MS and NMOSD anti-CD20 treated patients at the Pitié-Salpêtrière Hospital. Thus, we can assume that approximately 9000 MS or NMOSD patients were treated with anti-CD20 in France. Considering fingolimod, 10352 patients were treated with this drug in June 2021 (17.5% of MS treated patients)(5). Sixty percent of French MS patients had received a double dose of COVID-19 vaccine on July 18, 2021(6), but the exact proportion of vaccinated patients according to their treatment is not available. Furthermore, the variation of COVID-19 incidence rate and the appearance of COVID-19 new variants since the end of BNT162b2 randomized trial did not allow us to calculate and compare the expected number of MS and NMOSD post-vaccine COVID-19 cases per disease modifying therapies. However, in the COVISEP registry, the strikingly high proportion of anti-CD20 treated patients among post-vaccine cases (74.0%) while they were 20.0% among non-vaccinated COVID-19 is a strong argument to suspect that anti-CD20 exposure may be associated with a lower COVID-19 vaccination efficacy.

Due to the concerns regarding low immunogenicity of COVID-19 vaccines among anti-CD20 treated patients, French health authorities recommended on April 6, 2021 to perform a third dose four weeks after the second dose in anti-CD20 treated population. Our results reinforce this recommendation, even if we cannot be sure that this third dose would guarantee the same protection as vaccinated non-immunocompromised patients. In our series, one 44-year-old anti-CD20 treated patient was infected with COVID-19 despite triple dose vaccination and another 43-year-old patient treated with ocrelizumab

developed COVID-19 while she had been already infected more than one year before, and in the interim had received two doses of BNT162b2 vaccine. In contrast, among non-immunocompromised patients with previous evidence of COVID-19 infection, a single dose of mRNA vaccine is usually sufficient to induce a strong immunological response(7).

Among non-anti-CD20 treated patients, four COVID-19 post-vaccine patients were treated with fingolimod (23.5% of MS post-vaccine COVID-19, compared with 11.5% among non-vaccinated COVID-19). Even if this ratio difference is not as high as for anti-CD20, fingolimod represent a substantial part of post-vaccine COVID-19, while only one patient on interferon, and none on other DMT or untreated patient were recorded in the COVISEP registry.

To our knowledge, another case of COVID-19 after a double dose vaccination was previously described in a 52-year-old patient who had been vaccinated two weeks after his last ocrelizumab infusion(8). In our series, 3 patients had been vaccinated less than 3 months after the last anti-CD20 infusion. This short delay between infusion and vaccination may enhance the risk of vaccine inefficacy. Three patients without prior COVID-19 infection developed symptoms within 7 days after the second vaccine dose, thus before obtaining vaccine full efficacy based on the BNT162b2 randomized trial(9). However, in the BNT162b2 randomized trial, efficacy within 7 days after second dose was estimated to be 91%(9).

In this preliminary study, we observed that 72% of the patients with COVID-19 after double dose vaccine were treated with anti-CD20 therapies, while they represented only 20% of non-vaccinated COVID-19. This could prompt us to suspect that ocrelizumab and rituximab may not only impair COVID-19 vaccine humoral response, but more importantly may impair vaccination efficacy. However, we must keep in mind that due to public health decisions, MS patients treated with anti-CD20 were prioritized for COVID-19 vaccination since February 11, 2021. Thus, COVID-19 vaccine inefficacy in anti-CD20 treated patients may have been overstated in our study, as they may have been more quickly vaccinated than other DMT. However, this difference is decreasing over time, indeed, on 18 July 2021, 60% of all MS patients were vaccinated. Vaccination effectiveness assessment for other MS or NMOSD immunosuppressive

treatments (particularly fingolimod) warrants further longitudinal follow-up. As a limitation, we did not have information about COVID-19 vaccine serological response for post-vaccine COVID-19 cases. Importantly, despite occurring in immunocompromised patients, COVID-19 severity was mild in our series, except for one 67-year-old patient, and none of the patients died.

Conclusion

We describe 18 cases of COVID-19 infection occurring despite double dose BNT162b2 vaccine among patients with MS or NMOSD in the COVISEP registry, 13 of them were treated with anti-CD20 therapies. COVID-19 severity was mild. These preliminary findings stress the need for a prospective clinical and biological follow up on COVID-19 vaccine efficacy among this population exposed to immunosuppressive therapies, and further studies are needed to assess the impact of prior vaccination on COVID-19 severity among immunocompromised patients.

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Table 1: Characteristics of patients with COVID-19 occurrence despite double dose vaccination

Case	Diagnosis	Age (years)	EDSS	Comorbidity	Gender	Disease modifying therapy	Number of anti-CD20 cycles before vaccination	Immune globulin G levels before COVID-19 infection (g/L)	Delay Last anti-CD20 infusion – Vaccine 1st dose (weeks)	Vaccine type and number of doses	Delay 2nd or 3rd Dose vaccine – COVID-19 first symptoms (days)	COVID-19 severity
	COVID-19 symptoms > 7 days after BNT162b2 2nd dose											
1	MS	67	5.5	None	F	Rituximab	6	9.1	17	BNT162b2 2 doses	14	Hospitalized and receiving noninvasive ventilation or high-flow oxygen
2	MS	24	1	None	F	Ocrelizumab	1	8.9	30	BNT162b2 2 doses	13	Not hospitalized, limitation on activities
3	MS	35	0	None	F	Rituximab	2	10.2	98	BNT162b2 2 doses	20	Not hospitalized, limitation on activities
4	MS	31	3	None	M	Rituximab	8	12.1	3	BNT162b2 2 doses	55	Not hospitalized, limitation on activities
5	NMO AQP4	56	2.5	None	F	Rituximab	5	8.26	13	BNT162b2 2 doses	9	Not hospitalized, limitation on activities
6	MS	38	0	None	F	Rituximab	5	8.79	19	BNT162b2 2 doses	12	Not hospitalized, no limitations on activities
7	MS	47	6	None	F	Ocrelizumab	4	8.05	18	BNT162b2 2 doses	57	Not hospitalized, limitation on activities
8	MS	30	0	None	M	Ocrelizumab	4	10.96	19	BNT162b2 2 doses	86	Not hospitalized, limitation on activities
9	MS	48	2.5	None	F	Fingolimod	-	-	-	BNT162b2 2 doses	23	Hospitalized and did not required supplemental oxygen
10	MS	24	0	None	F	Fingolimod	-	-	-	BNT162b2 2 doses	45	Not hospitalized, limitation on activities
11	MS	32	0	None	F	Ocrelizumab	6	**NA**	13	BNT162b2 2 doses	61	Not hospitalized, limitation on activities
12	MS	28	0	None	F	Fingolimod	-	-	-	BNT162b2 2 doses	89	Not hospitalized, limitation on activities
13	MS	44	6	Diabetes	M	Rituximab	4	11.9	13	BNT162b2 3 doses	29 (after 3rd dose)	Not hospitalized, limitation on activities

14	MS	39	1	None	F	Fingolimod	-	-	-	BNT162b2 2 doses	71	Not hospitalized, limitation on activities
	COVID-19 symptoms ≤ 7 days after BNT162b2 2nd dose											
15	MS	34	1.0	None	F	Ocrelizumab	4	8.15	4	BNT162b2 2 doses	4	Not hospitalized, limitation on activities
16	MS	33	5	None	M	Rituximab	7	5.4	8	BNT162b2 2 doses	1	Not hospitalized, limitation on activities
17	MS	44	3.5	None	F	Interferon Beta	-	-	-	BNT162b2 2 doses	3	Not hospitalized, limitation on activities
18*	MS	43	6.5	None	F	Ocrelizumab	5	9.5	30	BNT162b2 2 doses	3	Not hospitalized, limitation on activities

EDSS: Expanded Disability Status Scale. MS: Multiple sclerosis. NMO: Neuromyelitis optica. Comorbidities: cardiovascular, pulmonary, diabetes, obesity (BMI>30), smoking.

*Patient N°18 had previously been infected with COVID-19 13 months before second infection, with laboratory evidence of anti-COVID-19 immunity.