MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Breakthrough SARS-CoV-2 infections in MS patients on disease-modifying therapies

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Multiple Sclerosis Journal

2022, Vol. 28(13) 2106–2111

DOI: 10.1177/13524585221102918

Abstract

Background: Patients with multiple sclerosis (pwMS) treated with anti-CD20 or fingolimod showed a reduced humoral response to SARS-CoV-2 vaccines.

Objective: In this study we aimed to monitor the risk of breakthrough SARS-CoV-2 infection in pwMS on different disease-modifying therapies (DMTs).

Methods: Data on the number of vaccinated patients and the number of patients with a breakthrough infection were retrospectively collected in 27 Italian MS centers. We estimated the rate of breakthrough infections and of infection requiring hospitalization per DMT.

Results: 19,641 vaccinated pwMS were included in the database. After a median follow-up of 8 months, we observed 137 breakthrough infections. Compared with other DMTs, the rate of breakthrough infections was significantly higher on ocrelizumab (0.57% vs 2.00%, risk ratio (RR) = 3.55, 95% CI = 2.74–4.58, $p < 0.001$) and fingolimod (0.58% vs 1.62%, RR = 2.65, 95% CI = 1.75–4.00, $p < 0.001$), while there were no significant differences in any other DMT group. In the ocrelizumab group the hospitalization rate was 16.7% versus 19.4% in the pre-vaccination era (RR = 0.86, $p = 0.74$) and it was 3.9% in all the other DMT groups versus 11.9% in the pre-vaccination period (RR = 0.33, $p = 0.02$).

Conclusions: The risk of breakthrough SARS-CoV-2 infections is higher in patients treated with ocrelizumab and fingolimod, and the rate of severe infections was significantly reduced in all the DMTs excluding ocrelizumab.

Keywords: Multiple sclerosis, COVID-19 vaccination, breakthrough infections

Date received: 1 March 2022; revised: 26 April 2022; accepted: 9 May 2022

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Introduction

Several recent studies evaluated the effect of vaccination against SARS-CoV-2 in patients with multiple sclerosis (pwMS) treated with disease-modifying therapies (DMTs). There is wide consensus that the use of anti-CD20 monoclonal antibodies and fingolimod are associated with an impaired virus-specific humoral immune response compared with all the other DMTs.[1–4] On the contrary, there is also growing evidence that vaccinated pwMS treated with anti-CD20 generated robust virus-specific CD4 and CD8T cell responses,[4,5] while these are slightly reduced in fingolimod treated patients.[5] Previous studies indicated higher rates of breakthrough infections in pwMS under anti-CD20 and fingolimod therapies,[6–8] suggesting a relevant role of antibodies in preventing the infection.

Against this background and taking advantage of the large network of multiple sclerosis (MS) centers within the Italian Alliance against COVID-19 promoted by the Italian MS Society, we collected data from 27 Italian MS centers on the number of vaccinated patients and the number of patients who had a breakthrough infection in each DMT group, in the period preceding the spread of the Omicron variant,

that started its massive diffusion in Italy after the December 2021 holiday season. The aim of this study is to estimate the rate of breakthrough infections per DMT class on a large sample of vaccinated pwMS and to compare the rates of severe infections with the rate observed in Italy in the pre-vaccination era.[9]

Method

Study design and participants

This was a retrospective data collection conducted in 27 Italian MS centers on pwMS undergoing the SARS-CoV-2 vaccination. The vaccination campaign started in Italy in December 2020, and pwMS were vaccinated with mRNA vaccines (BNT162b2—Pfizer BioNTech or mRNA-1273—Moderna Tx, Inc.). The second dose was scheduled 21 days after the first dose. A third booster dose started to be delivered in November 2021 and was recommended to pwMS 4 months after the second dose. A fourth dose is now planned for fragile patients, but its delivery has not started yet in Italy. The third dose was an mRNA vaccine, with no relationship with the two previously received doses. There was the advice to maximize the time from last infusion to vaccination for patients on anti-CD20, but the strategy was managed at each MS center.

Each MS center was requested to report the number of pwMS who received a full vaccination cycle (two or three mRNA vaccine doses (BNT162b2—Pfizer BioNTech or mRNA-1273—Moderna Tx, Inc.), or one vaccine dose and a certified COVID-19 infection) in each DMT group from March 2021 to 25 December 2021. Data cutoff was set before the spread of the Omicron variant in Italy, since on 23 December 2021 the percentage of Omicron infections was estimated to be 28% (https://www.iss.it/primo-piano, accessed on 25 December 2021). Breakthrough infections occurred within 8 months, defined as a PCR-confirmed test after 14 days from the second or the third vaccine dose, were extracted from the platform dedicated to COVID-19 data collection in pwMS (MuSC-19 database)[10] for the participating centers. The post-vaccination SARS-CoV-2 infection was recorded in a dedicated Case Report Form (CRF).

The study is done in compliance with the principles of the Declaration of Helsinki. The study was approved by the regional ethics committee of Liguria (University of Genoa; n 130/2020–DB id 10433) and at a national level by the Italian Medicines Agency. Written informed consent was obtained from all participants before starting any study procedures.

Primary outcome: breakthrough infection

The primary objective of this analysis was to compare the incidence of breakthrough SARS-CoV-2 infections among the vaccinated pwMS in each DMT group. The follow-up time is calculated since the last vaccine dose. Breakthrough infections were defined as a PCR-confirmed test after 14 days from the second or the third vaccine dose, or from the first dose in case of previous COVID-19 infection.

Statistical analysis

The percentage of patients with a breakthrough infection in the different DMT groups was calculated: 95% confidence intervals (CI) were estimated using the normal approximation to the binomial calculation.[11] The difference in rate of infections between DMT groups were estimated by risk ratios (RRs) and evaluated by chi-square tests. Since the protecting effect of vaccination is expected to vanish with time, we split the 8 month follow-up into two periods of 4 months. The difference in rate of infections in the first 4 months versus the second 4 months of follow-up were estimated by ORs and evaluated by the McNemar test for paired data. The hospitalization rate was compared with the pre-vaccination rate reported in Italy by a chi-square test.[9]

Results

Data were collected between 1 March 2021 and 24 December 2021. A total of 19,641 pwMS who had a full vaccination cycle with an mRNA vaccine (2 or 3 vaccine dose, or 1 vaccine dose after COVID-19 infection) were included in the database. The number of vaccinated pwMS in each DMT group is reported in Table 1. The mean follow-up time was 249 days (range 99–354). Among them, 137 breakthrough infections were observed (26 (19.0%) after the third dose, 1 after COVID-19 infection and one dose) over a mean interval after the last vaccine dose of 142 days (range 14–262) (Table 1). Over the whole follow-up of about 8 months, we compared the proportion of patients with breakthrough infections in each DMT group with the pooled proportion of the patients on all the other DMTs (Figure 1, panel a). The rate of breakthrough infections was significantly higher in patients treated with ocrelizumab (2.00%, 95% CI = 1.36–2.66) than in patients treated with all the other DMTs (0.57%, 95% CI = 0.46%–0.68%) with an RR = 3.55, 95% CI = 2.74–4.58, $p < 0.001$; the same was observed in patients treated with fingolimod who had a higher rate of breakthrough infections (1.62%, 95% CI = 1.02%–2.21%) than the patients treated with all the other DMTs (0.61%, 95%

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Table 1. Characteristics of patients with breakthrough infections ($N=137$).

Female sex		85 (62.0)
Age, years		42.3 ± 10.70
BMI (kg/m^2)		24.6 ± 4.95
MS phenotype	Primary progressive	9 (6.6)
	Relapsing remitting	116 (84.7)
	Secondary progressive	7 (5.1)
	Missing data	5 (3.6)
Disease duration, months		99.5 (44.0–182.0)
Last EDSS before COVID-19 infection		2.0 (1.0–3.5)
Relapse in the 6 months before COVID-19 infection		7 (5.1)
Number of breakthrough infections in each DMT/ number of vaccinated patients, (%)	Alemtuzumab	0/371 (0.0)
	Azathioprine	0/298 (0.0)
	Cladribine	4/570 (0.70)
	Dimethyl fumarate	22/2668 (0.82)
	Fingolimod	28/1733 (1.61)
	Glatiramer acetate	4/1514 (0.26)
	Interferon	7/2452 (0.29)
	Natalizumab	15/1843 (0.81)
	Ocrelizumab	36/1794 (2.00)
	Rituximab	3/364 (0.82)
	Teriflunomide	10/1379 (0.73)
	Other	0/389 (0.0)
	Untreated	8/4266 (0.19)
Boost COVID-19 vaccination		26 (19.0)
Heterologous vaccine[a]		4 (2.9)
Covid severity	(0) Uninfected, no viral RNA detected	0 (0.0)
	(1) Asymptomatic, viral RNA detected	16 (11.8)
	(2) Symptomatic, independent	95 (69.3)
	(3) Symptomatic, assistance needed	16 (11.8)
	(4) Hospitalized, no oxygen therapy	4 (2.9)
	(5) Hospitalized, oxygen by mask or nasal prongs	5 (3.7)
	(6) Hospitalized, oxygen by NIV or high flow	0 (0.0)
	(7) Intubation and mechanical ventilation, $piO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	1 (0.7)
	(8) Mechanical ventilation, $pO_2/FIO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	0 (0.0)
	(9) Mechanical ventilation, $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	0 (0.0)
	(10) Died	0 (0.0)

MS: multiple sclerosis; BMI: body mass index; EDSS: Expanded Disability Status Scale; DMT: disease-modifying therapy. "Other DMT" = mitoxantrone, methotrexate, siponimod.
Results are expressed as count (%), mean ± standard deviation, or median (interquartile range), as appropriate.
Covid severity has been defined according to clinical progression scale (10 points) provided by the WHO Working Group.[12]
[a]Heterologous vaccine = two doses of Pfizer vaccine followed by a booster of Moderna.

CI = 0.50–0.72) with an RR = 2.65, 95% CI = 1.75–4.00, $p < 0.001$. Among those who had the infection after the third dose, 10 (38%) were in ocrelizumab, 8 (31%) in fingolimod, and 8 (31%) in other DMTs.

Among the patients who had the SARS-CoV-2 infection, 10 (7.3%) had a severe disease course and were hospitalized. Six patients treated with ocrelizumab were hospitalized and in this group the rate of hospitalization was 16.7%, slightly lower but not significantly different than the pre-vaccination rate observed in Italy (19.4%) in the same DMT group[9] (relative reduction = 14%, RR = 0.86, 95% CI = 0.38–1.91, $p = 0.74$). In the fingolimod group we observed

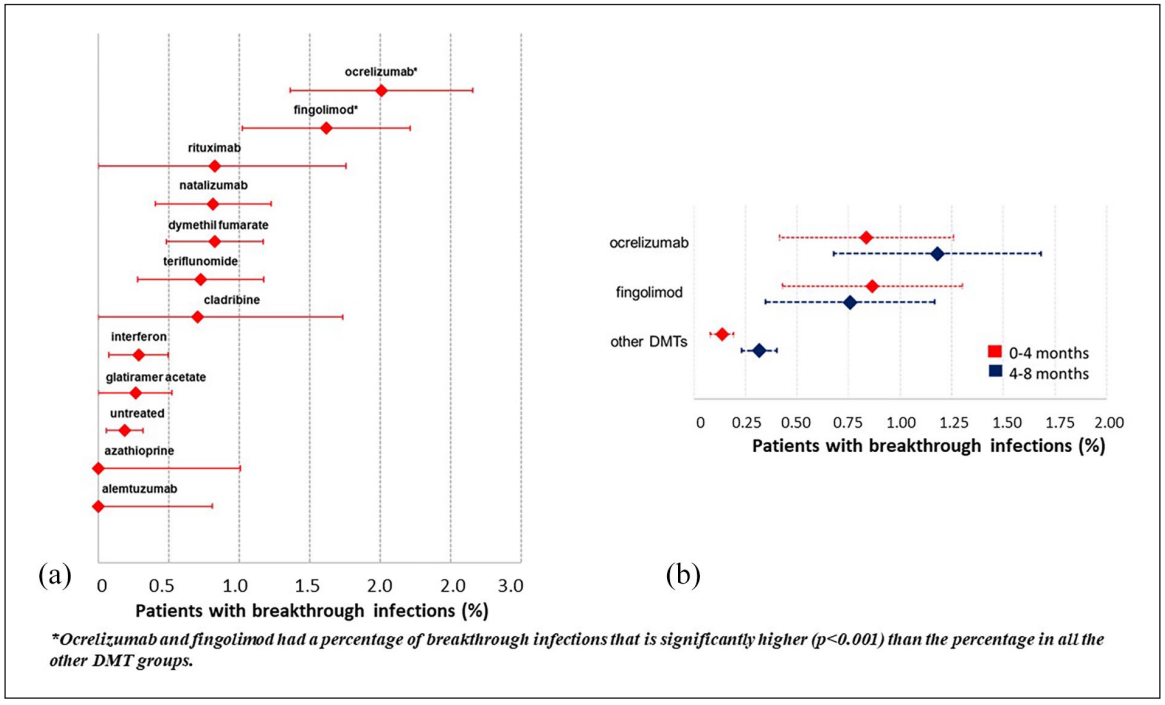

Figure 1. (a) Cumulative incidence of breakthrough infections in patients in each DMT group and (b) breakthrough infection rates according to time since vaccination in ocrelizumab, fingolimod, and other DMTs.

just one hospitalized patient (3.6%). The rate of hospitalization was 3.9% in all the other DMT groups as compared with 11.9% in the pre-vaccination period[9] (relative reduction = 67%, RR = 0.33, 95% CI = 0.13–0.88, $p = 0.02$). One patient in ocrelizumab was admitted to the intensive care unit (ICU) and recovered. Only one patient (in ocrelizumab) who had the infection after the third dose was hospitalized.

Figure 1(b) shows the rate of breakthrough infections in two time periods of equal duration: the first 4 months following the last vaccination dose versus the period of 4–8 months after the last vaccination dose in patients treated with ocrelizumab, fingolimod, and all the other DMTs. The rate in patients treated with ocrelizumab and fingolimod was not significantly affected by the time since vaccination (ocrelizumab: 0–4 months after vaccination: 0.84%, 4–8 months after vaccination: 1.18%, odds ratio (OR) = 1.40, $p = 0.31$; fingolimod: 0–4 months after vaccination: 0.86%, 4–8 months after vaccination: 0.76%, OR = 0.88, $p = 0.75$). In all the other DMT groups the rate is much lower (0–4 months after vaccination: 0.14%) and it was significantly increased after 4 months from the last vaccine dose (4–8 months after vaccination: 0.32%, OR = 2.32, 95% CI = 1.38–4.01, $p < 0.001$).

Discussion

Previous smaller studies indicated higher rates of breakthrough infections in patients on anti-CD20 therapy or on fingolimod,[6] suggesting a relevant role of antibodies in preventing the infection. The clinical follow-up of the CovXiMS study[1] evaluating humoral response in 1705 pwMS, who received two doses of mRNA vaccines,[8] reported 30 breakthrough infections over a 6-month follow-up, during the delta wave. The risk of infection was associated with lower SARS-CoV-2 antibody levels measured after 4 weeks from the second vaccine dose.[9]

This study on a large sample of pwMS who received a full vaccination cycle confirms that the risk of contracting SARS-CoV-2 infection after COVID-19 mRNA vaccines is higher in pwMS on anti-CD20 monoclonal antibodies or fingolimod. We observed just one admission to ICU and no deaths. There are some limitations of this study that are intrinsic to its retrospective nature, which must be acknowledged upfront. We cannot evaluate how many patients were tested for COVID-19 and were negative. It is therefore possible, given the increased vigilance among patients treated with B-cell depleting therapies, that they were being tested more often. Also, it is possible that additional mild or asymptomatic cases with

positive home antigen tests were not recorded in the database. The COVID-19 cases were reported by neurologists, but there was no planned screening nor were they called on a regular basis to assess for infections, symptoms, and testing.

Despite the small sample of 137 infections, three results emerge. First, in our cohort, patients treated with fingolimod and ocrelizumab had a higher breakthrough infection rate than patients on other drugs. The number of patients on rituximab is too small to draw conclusions about them, since just one additional infection would have drastically changed the rate of infection estimate. Second, among the infected patients after vaccination treated with ocrelizumab the hospitalization rate is very similar to the hospitalization rate of patients on the same treatment in the pre-vaccination era,[8] while it is reduced by 67% in pwMS in other DMTs. However, we must consider that this result can be confounded by an increased propensity of clinicians to admit to hospital pwMS on ocrelizumab who develop COVID-19, because of previous studies showing that these patients are at a higher risk for a severe course.[8] Moreover, a larger sample is needed to draw conclusions on the impact of vaccination on hospitalization rate in patients treated with ocrelizumab. Third, as expected,[9] the vaccine-induced protection from the disease is waning with time since vaccination, and this is more evident in patients treated with DMTs other than ocrelizumab and fingolimod, who already had low antibody levels soon after the vaccination. In fact, while the infection rate is similar in the first and in the second 4 months after vaccination in patients on ocrelizumab and fingolimod, and consistently higher than in patients on other DMTs, the initial protective effect is vanishing with time for patients in the other DMTs group, who had a good level of antibody response 4 weeks after vaccination.[1] A major limitation of this study is the lack of immunological data that preclude the possibility to correlate the timing of vaccination with the last infusion date for patients treated with ocrelizumab. These data would have been useful for confirming the optimal timing for vaccination for these patients.

This study complements the information of previous studies reporting the antibody levels after anti-SARS-Cov-2 vaccination in pwMS on different DMTs,[1–7] suggesting that antibodies play a dominant role in preventing COVID-19 infections.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: P.A. received honoraria for lecturing and participation in advisory boards, and/or travel expenses for attending congresses and meetings from Almirall, Biogen, BMS-Celgene, Merck, Novartis, Roche, Sanofi-Genzyme, Teva Italia, and Viatris. S.B. received speaker and/or advisor's board fee from Biogen, Novartis, Roche, Viatris, and Merck Serono. F.C. received honoraria for advisory board and/or for public speaking, and/or travel grant, from Biogen, Merck, Teva, Novartis, Sanofi-Genzyme, and Roche. P.C. has received advisory board membership, speaker honoraria, or travel grants to attend national and international conferences from Biogen, Merck Serono, Teva, Roche, Novartis, Cellgene-BMS, and Sanofi-Genzyme. M.C. received grants and consulting fees from Merck, Biogen, Novartis, Sanofi-Genzyme, Roche, and Almirall. G.C., L.P., E.C., M.T.F., G.L., M.T.R., and M.L.S. have nothing to disclose. A.C. reports speaking honoraria from Merck, Sanofi, Novartis, Biogen, Roche, Bristol Myers Squibb, Almirall and has received research support from Roche, Biogen, and Merck. C.C. received personal compensation for advisory board and speaking for Merck Serono, Novartis, Almirall, Biogen, and Roche. M.D.F. participated on advisory boards for and received research support, speaker/writing honoraria, and funding for traveling from Bayer, Biogen Idec, Genzyme, Merck, Mylan, Novartis, Roche, Teva, and Viatris. A.D.S. received personal compensation for speaking and consulting by Biogen, Novartis, and Genzyme and has been reimbursed by Merck, Biogen, Genzyme, and Roche for attending several conferences. R.D. received grants from Roche, Novartis, Biogen, Merck, Viatris, and Genzyme. D.F. received travel grants and/or speaker/advisory board honoraria from Biogen, Roche, Novartis, TEVA, Sanofi Genzyme, and Merck Serono. P.I. reports personal fees from Roche, Biogen, and Merck. R.I. received speaker honoraria and/or consultancy from Biogen, Teva, Genzyme, Merck, Almirall, and Roche. R.L. received personal compensations for speaking or consultancy from Biogen, Teva, Genzyme, Merck, Mylan, Novartis, and Roche. A.L. received personal compensations from Merck, Biogen, Novartis, Roche, and Almirall. F.P. received personal compensation for serving on advisory board Almirall, Bayer, Biogen, Bristol Meyers Squibb, Merck, Novartis, Roche, and Sanofi; he further received unrestricted research grants by Biogen, Merck, Roche, FISM, University of Catania, and Reload (onlus patients association). F.R. received speaker and/or advisors board fee from Merck, Novartis, Biogen, and Genzyme. M.S. reports grants and personal fees from Biogen, Merck, Novartis,

Roche, Sanofi, and Teva, grants from the Italian Multiple Sclerosis Foundation, and from Sapienza University of Rome. I.S. received consulting fees from Hippocrates Research, NovaNeuro, Sakura Italia, ADL Farmaceutici, and Associazione Commissione Difesa Vista Onlus. E.S. received speaker honoraria and/or consultancy from Biogen, Teva, Genzyme, Merck, Novartis, Almirall, and Roche. M.P.S. received consulting fees from Merck, Biogen, Novartis, Sanofi, Roche, Geneuro, GSK, Medday, and Immunic. M.U. received consulting fees from Biogen, Novartis, and Serono.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by FISM (2021/Special-Multi/001).

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Supplemental Material

Supplemental material for this article is available online.

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