

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

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60 **Abstract**

61 **Background.** Patients with Multiple Sclerosis (pwMS) treated with anti-CD20 or fingolimod showed a
62 reduced humoral response to SARS-CoV-2 vaccines. In this study we aimed to monitor the risk of
63 breakthrough SARS-CoV-2 infection in pwMS on different Disease Modifying Therapy (DMT).

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

67 **Findings.** 19641 vaccinated pwMS were included in the database. After a median follow-up of 8 months, we
68 observed 137 breakthrough infections. As compared to the other DMTs, the rate of breakthrough infections
69 was significantly higher on ocrelizumab (0.57% vs 2.00%, RR=3.55,95%CI=2.74-4.58, p<0.001) and
70 fingolimod (0.58% vs 1.62%, RR=2.65,95%CI=1.75-4.00, p<0.001), while there were no significant
71 differences in any other DMT group. In the ocrelizumab group the hospitalization rate was 16.7% vs 19.4%
72 in the pre-vaccination era (RR=0.86,p=0.74) and it was 3.9% in all the other DMT groups vs 11.9% in the
73 pre-vaccination period (RR=0.33,p=0.02).

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

78 **Introduction**

79 Several recent studies evaluated the effect of vaccination against SARS-CoV-2 in patients with multiple
80 sclerosis (pwMS) treated with disease-modifying therapies (DMTs). There is wide consensus that the use of
81 anti-CD20 monoclonal antibodies and fingolimod are associated with an impaired virus-specific humoral
82 immune response as compared to all the other DMTs¹⁻⁴. On the other hand, there is also growing evidence
83 that vaccinated pwMS treated with anti-CD20 generated robust virus specific CD4 and CD8 T cell
84 responses⁴⁻⁵, while these are slightly reduced in fingolimod treated patients⁵. A preliminary follow-up study
85 of 344 fully vaccinated pwMS on DMT reported 13 breakthrough infections, 10 of which were in patients on
86 anti-CD20 therapy and the remaining 3 on fingolimod⁶, suggesting a relevant role of antibodies in preventing
87 the infection. The French registry recently reported a case series of 18 pwMS who had Covid-19 after two
88 doses of BNT162b2-vaccination, 13 of which treated with anti-CD20 and four with fingolimod⁷. Finally, the
89 clinical follow up of the CovXiMS study¹ evaluating humoral response in 1705 pwMS who received two
90 doses of mRNA vaccines⁸, reported 23 breakthrough infections over a 6 month follow up. The risk of
91 infection was associated with lower SARS-CoV-2 antibody levels measured after 4 weeks from the second
92 vaccine dose⁸.

93 Against this background and taking advantage of the large network of MS centers within the Italian Alliance
94 against Covid-19 promoted by the Italian MS Society, we collected data from 27 Italian MS centers on the
95 number of vaccinated patients and the number of patients who had a breakthrough infection in each DMT
96 group, in the period preceding the spread of the Omicron variant, that started its massive diffusion in Italy
97 after the December 2021 holiday season. Aim of this study is to estimate the rate of breakthrough infections
98 per DMT class on a large sample of vaccinated pwMS and to compare the rates of severe infections to the
99 rate observed in Italy in the pre-vaccination era⁹.

101 **Patients and Methods**

102 *Study design and participants*

103 This was a retrospective data collection conducted in 27 Italian MS centers on pwMS undergoing the SARS-
104 CoV-2 vaccination. Each MS center was requested to report the number of pwMS vaccinated by two mRNA
105 vaccine doses (BNT162b2 (Pfizer Inc, and BioNTech), or mRNA-1273 (Moderna Tx, Inc)) in each DMT
106 group from March 2021 to December 25, 2021. Data cutoff was set before the spread of the Omicron variant
107 in Italy, since on December 23, 2021 the percentage of Omicron infections was estimated to be 28%
108 (<https://www.iss.it/primo-piano>, accessed on December 25, 2021). Breakthrough infections occurred within
109 8 months, defined as a PCR-confirmed test after 14 days from the second or the third vaccine dose, were
110 extracted from the platform dedicated to Covid-19 data collection in pwMS (MuSC-19 database¹⁰) for the
111 participating centers. The post-vaccination SARS-CoV-2 infection was recorded in a dedicated Case Report
112 Form (CRF).

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

117 *Primary Outcome: breakthrough infection*

118 The primary objective of this analysis was to compare the incidence of breakthrough SARS-CoV-2
119 infections among the vaccinated pwMS in each DMT group. These conditions entail a PCR-confirmed
120 swab, and a time lag of at least 14 days from a full vaccination cycle (after the second or third vaccination
121 dose, or after the first dose following a Covid-19 infection).

122 *Statistical analysis*

123 The percentage of patients with a breakthrough infection in the different DMT groups was calculated. 95%
124 Confidence Intervals (CI) were estimated using the normal approximation to the binomial calculation¹¹.
125 Difference of rate of infections between DMT groups were estimated by Risk Ratios (RR) and evaluated by
126 Chi-square tests. Difference of rate of infections in the first 4 months vs the second 4 months of follow up
127 were estimated by ORs and evaluated by the McNamar test for paired data.

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130

131 **Results**

132 Data were collected between March 1, 2021 and December 24, 2021. 19641 pwMS who had a full
133 vaccination cycle with an mRNA vaccine (2 or 3 vaccine dose, or 1 vaccine dose after Covid-19 infection)
134 were included in the database. The number of vaccinated pwMS in each DMT group is reported in Table 1.
135 The mean follow-up time was 249 days (range 99-354). Among them, 137 breakthrough infections were
136 observed (26 (19.0%) after the third dose, 1 after Covid-19 infection and one dose) over a mean interval after
137 the last vaccine dose of 142 days (range 14-262) (Table 1). Over the whole follow-up of about 8 months, we
138 compared the proportion of patients with breakthrough infections in each DMT group to the pooled
139 proportion of the patients on all the other DMTs (Figure 1, panel A). The rate of breakthrough infections
140 was significantly higher in patients treated with ocrelizumab (2.00%, 95%CI=1.36-2.66) than in patients
141 treated with all the other DMTs (0.57%, 95%CI=0.46%-0.68%) with a RR=3.55, 95%CI=2.74-4.58,
142 $p<0.001$; the same was observed in patients treated with fingolimod who had a higher rate of breakthrough
143 infections (1.62%, 95%CI= 1.02%-2.21%) than the patients treated with all the other DMTs (0.61%,
144 95%CI=0.50-0.72) with a RR=2.65, 95%CI= 1.75-4.00, $p<0.001$. Among the patients who had the SARS-
145 CoV-2 infection, 10 (7.3%) had a severe disease course and were hospitalized. Six patients treated with
146 ocrelizumab were hospitalized and in this group the rate of hospitalization was 16.7%, slightly lower but not
147 significantly different than the pre-vaccination rate observed in Italy (19.4%) in the same DMT group⁷
148 (relative reduction=14%, RR=0.86, 95%CI=0.38-1.91, $p=0.74$). In the fingolimod group we observed just 1
149 hospitalized patient (3.6%). The rate of hospitalization was 3.9% in all the other DMT groups as compared to
150 11.9% in the pre-vaccination period⁷ (relative reduction=67%, RR=0.33, 95%CI=0.13-0.88, $p=0.02$). One
151 patient in ocrelizumab was admitted to the Intensive Care Unit (ICU) and recovered.

152 Figure1, panel B, reports the rate of breakthrough infections in two time periods of equal duration: the first 4
153 months following the last vaccination dose vs the period 4-8 months after the last vaccination dose in
154 patients treated with ocrelizumab, fingolimod and all the other DMTs. The rate in patients treated with

155 ocrelizumab and fingolimod was not significantly affected by the time since vaccination (ocrelizumab: 0-4
156 months after vaccination: 0.84%, 4-8 months after vaccination: 1.18%, OR=1.40, p=0.31; fingolimod: 0-4
157 months after vaccination: 0.86%, 4-8 months after vaccination: 0.76%, OR=0.88, p=0.75). In all the other
158 DMT groups the rate is much lower (0-4 months after vaccination: 0.14%) and it was significantly increased
159 after 4 months from the last vaccine dose (4-8 months after vaccination: 0.32%, OR=2.32, 95%CI=1.38-
160 4.01, p<0.001).

161 Discussion

162 This study on a large sample of pwMS who received a full vaccination cycle confirms that the risk of
163 contracting SARS-CoV-2 infection after Covid-19 m-RNA vaccines is higher in pwMS on anti-CD20
164 monoclonal antibodies or fingolimod. We observed just one admission to ICU and no deaths. Despite the
165 small sample of 137 infections, two results emerge. First, in our cohort, among the infected patients after
166 vaccination treated with ocrelizumab the hospitalization rate is very similar to the hospitalization rate of
167 patients on the same treatment in the pre-vaccination era⁸, while it is reduced by 67% in pwMS in other
168 DMTs. However, we must consider that this result can be confounded by an increased propensity of clinician
169 to admit to hospital pwMS on ocrelizumab who develop Covid-19, because of previous studies showing that
170 these patients are at a higher risk for a severe course⁸. Second, as expected⁹, the vaccine-induced protection
171 from the disease is waning with time since vaccination, and this is more evident in patients treated with
172 DMTs other than ocrelizumab and fingolimod, who already had low antibody levels soon after the
173 vaccination. In fact, while the infection rate is similar in the first and in the second four months after
174 vaccination in patients on ocrelizumab and fingolimod, and consistently higher than in patients on other
175 DMTs, the initial protective effect is vanishing with time for patients in the other DMTs group, who had a
176 good level of antibody response four weeks after vaccination¹. This study complements the information of
177 previous studies reporting the antibody levels after anti-SARS-Cov-2 vaccination in pwMS on different
178 DMTs¹⁻⁷, suggesting that antibodies play a dominant role in preventing Covid-19 infections and their severe
179 consequences.

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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/m²)		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 six 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		4 (2.9)
Covid severity	Asymptomatic, viral RNA detected	16 (11.8)
	Symptomatic, independent	95 (69.3)
	Symptomatic, assistance needed	16 (11.8)
	Hospitalized, no oxygen therapy	4 (2.9)
	Oxygen by mask or nasal prongs	5 (3.7)
	Intubation and mechanical ventilation,	
	piO ₂ /FiO ₂ ≥150 or SpO ₂ /FiO ₂ ≥200	1 (0.7)

Results are expressed as count (%), mean ± Standard Deviation, or median [Inter Quartile Range], as appropriate.

MS=Multiple Sclerosis, BMI=Body Mass Index, EDSS=Expanded Disability Status Scale, DMT=Disease Modifying Therapy

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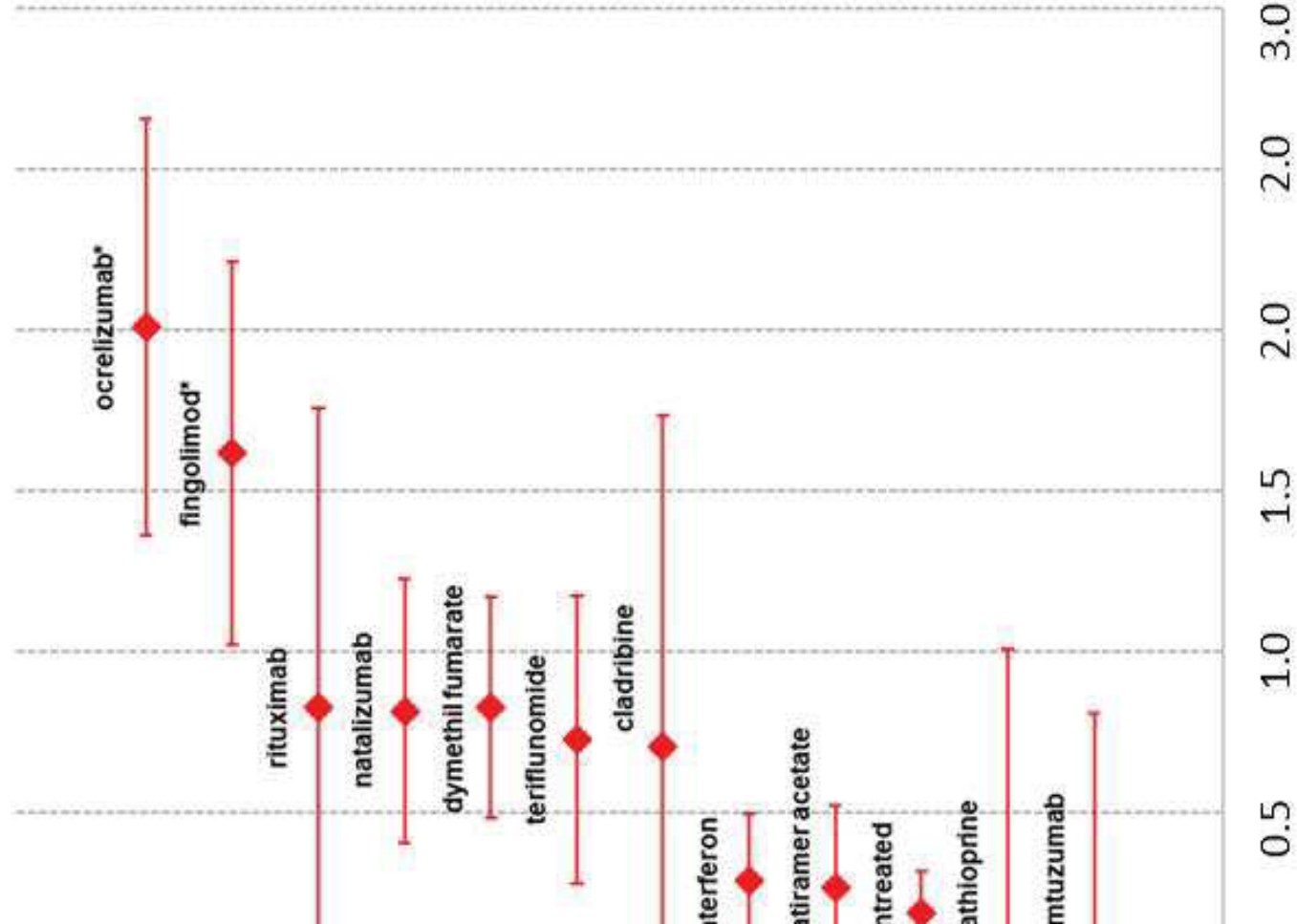
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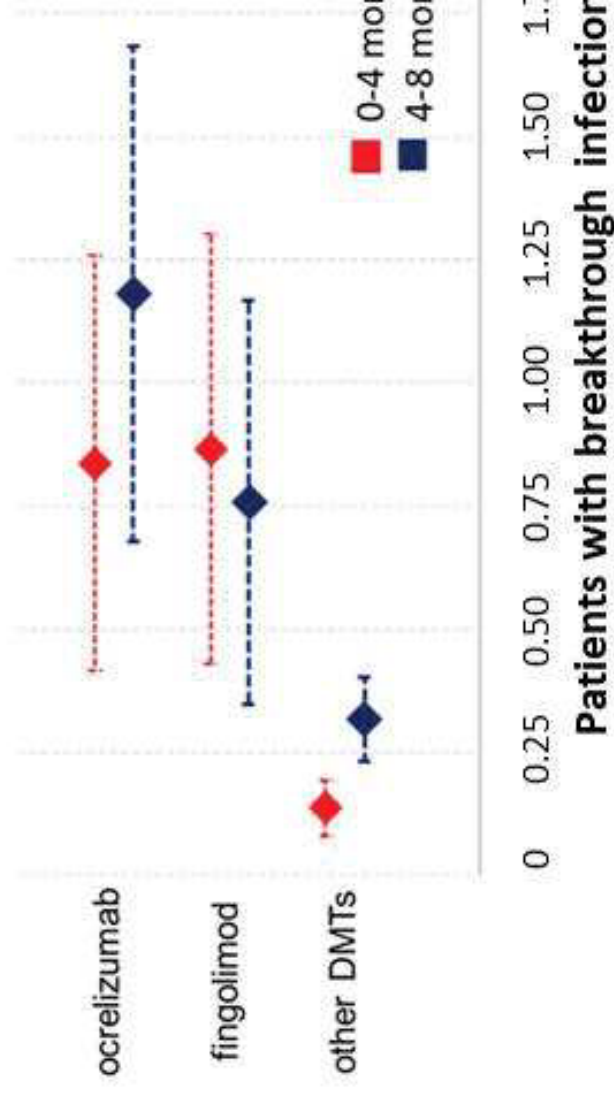
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Figure legends

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



B



Patients with breakthrough infections that is significantly higher ($p < 0.001$) than the percentage in the control group.