

# mRNA COVID-19 vaccines do not increase the short-term risk of clinical relapses in multiple sclerosis

## INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system. A novel coronavirus, namely SARS-CoV-2, has been recently responsible for the highly infectious disease referred as COVID-19, rapidly spreading all over the world. Many vaccines have been developed to control COVID-19 pandemic, including the mRNA vaccines Pfizer/BioNTech (BNT162b2) and Moderna (mRNA1273).<sup>1</sup> The vaccination of people with MS (pwMS) has been recommended by several national and international MS societies. However, effectiveness and safety of anti-COVID-19 mRNA vaccines in MS need to be confirmed. The aim of this study was to evaluate the short-term risk of clinical relapses in pwMS in the 2 months after the first administration of an mRNA COVID-19 vaccine.

## PATIENTS AND METHODS

Twenty-five Italian MS tertiary centres participated to this prospective, self-controlled, multicentric observational study. In Italy, COVID-19 population vaccination started at the end of December 2020 and first involved healthcare professionals. All pwMS, diagnosed according to McDonald's 2017 criteria, who underwent the first dose of an mRNA COVID-19 vaccine within January 2021 were recruited from each participating centre. All patients received Pfizer/BioNTech BNT162b2 vaccine according to vaccine availability in Italy. Database lock was planned on 31 March so that all patients were followed for at least 2 months after the first dose. The following data were collected: (1) sex; (2) age and disease duration; (3) disease course (relapsing remitting; secondary progressive; primary progressive); (4) disability score (Expanded Disability Status Scale, EDSS); (5) clinical relapses in the year before vaccination, with specific regard to the 2

months immediately preceding vaccination; (6) MRI activity in the year before vaccination (new T2 or Gd enhancing—Gd+—lesions); (7) previous molecular swab confirmed SARS-CoV-2 infection; (8) vaccine administration date and (9)

**Table 1** Characteristics of the cohort

Demographic features	
Number	324
Age (years)	42.7±10.8
Gender (female)	242 (74.7%)
Clinical characteristics	
Disease course: RR	303 (93.5%)
SP	15 (4.6%)
PP	6 (1.9%)
Disease duration (years)	11.9±8.5
EDSS Score at the time of vaccination	2.1±1.5
DMTs at the time of vaccination	
Glatiramer acetate	21 (6.5%)
Interferons	52 (16.0%)
Dimethyl fumarate	84 (25.9%)
Teriflunomide	20 (6.2%)
Fingolimod	31 (9.6%)
Natalizumab	37 (11.4%)
Cladribine	9 (2.8%)
Ocrelizumab	31 (9.6%)
Siponimod	1 (0.3%)
Alemtuzumab	5 (1.5%)
Rituximab	5 (1.5%)
Azathioprine	1 (0.3%)
Methotrexate	1 (0.3%)
No therapy	26 (8.0%)

Continuous variables are reported as mean±SD. Categorical variables are reported as number (percentage). DMTs, disease-modifying treatments; EDSS, Expanded Disability Status Scale; PP, primary progressive; RR, relapsing remitting; SP, secondary progressive.

disease-modifying treatments at the time of vaccination. The presence, characteristics and number of relapses in the 60 days after the first administration of the vaccine were recorded. A relapse was defined as a clinical episode suggestive of demyelination developing acutely or subacutely, with a duration of at least 24 hours in the absence of fever or infection. The interval between vaccination and clinical relapse was calculated.

## STATISTICAL ANALYSIS

Continuous variables are reported as mean±SD, while categorical variables are reported as count and percentages. To test the difference between relapses incidence in the 2 months before and after vaccination, we fitted a paired negative binomial model. Demographical and clinical variables (age, gender, disease duration and EDSS) were also included as covariates. For all the tests, significance was set at a *p* value <0.05.

## RESULTS

We included 324 pwMS exposed to the Pfizer/BioNTech BNT162b2 vaccine. Cohort characteristics are reported in [table 1](#). Overall, 28 out of 324 (8.6%)

patients had experienced SARS-CoV-2 infection confirmed by a molecular swab (224.8±103.5 days before the first dose of vaccination). Overall, 322/324 patients (99.4%) underwent both the doses of the vaccine with an interval between doses of 21.5±4 days. Two patients did not complete the vaccination schedule: one because of the evidence of SARS-CoV-2 infection after the first dose and the other because of the evidence of radiological activity without clinical relapses in an already planned MRI scan, 3 days after the first dose, for which the second vaccine dose was postponed. In the 2 months before vaccination, six clinical relapses were reported in 6 out of 324 patients (1.9%). In the 2 months after vaccination, seven clinical relapses occurred in 7/324 patients (2.2%). The incidence of relapses in the 2 months before and after vaccination was not statistically different (*B*=0.154, 95% CI -0.948 to 1.288, *p*=0.78). Also, demographical (age, gender) and clinical disease characteristics (disease duration, EDSS) had no effect on relapses occurrence. Five of the relapsing patients were women. Five relapses were monofocal and two were multifocal. The mean time interval between the first dose of vaccination and the clinical relapse was 44±11.6 days. At the time of vaccination, three patients were treated with dimethyl fumarate, one with glatiramer acetate, two with ocrelizumab and one was not treated.

## DISCUSSION

Vaccines safety in pwMS has been matter of debate.<sup>2-4</sup> In the current COVID-19 pandemic scenario, the availability of mRNA vaccines warrants the urgent need to define their safety in pwMS. Our preliminary analysis demonstrated that the Pfizer/BioNTech BNT162b2 vaccine does not increase the short-term risk of clinical reactivation in pwMS. Recently, Achiron *et al* reported in an observational study on 555 pwMS a similar rate of patients with acute relapse after Pfizer/BioNTech BNT162b2 vaccine. No increased risk of relapse activity was estimated comparing that cohort with a cohort of non-vaccinated patients evaluated in the same period in the prepandemic era.<sup>5</sup> The latter study, however, suffers of the limitation of an heterogeneous follow-up period (about 20% of patients with relapses were followed for less than 14 days after immunisation) which might have lowered the number of recorded relapses. Our study is the first prospective study including a large cohort of patients with MS who were followed, with a self-controlled design,

for at least 2 months after the first dose of the Pfizer/BioNTech BNT162b2 vaccine. A limit of our study, mainly related to its real life context, is the lack of MRI data, which might prevent the detection of potential MRI activity in absence of clinical relapses, as well as the short-term follow-up. Larger observational studies with longer follow-up would be desirable. Moreover, due to the low number of patients with progressive MS in the cohort (21 out of 324 subjects, 6.5%), no clear conclusions can be drawn on the effects of Pfizer/BioNTech BNT162b2 vaccination on disease worsening in progressive MS. Despite these limitations, we think that the results of our study can improve clinical practice driving clinical decisions and support the recommendation to promote access of pwMS to COVID-19 vaccination.

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