

Impact of COVID-19 vaccination or infection on disease activity in a radiologically isolated syndrome cohort: The VaxiRIS study

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Abstract

Background: Vaccination in patients with multiple sclerosis (MS) treated with immunosuppressive drugs is highly recommended. Regarding COVID-19 vaccination, no specific concern has been raised.

Objectives: We aimed to evaluate if COVID-19 vaccination or infection increased the risk of disease activity, either radiological or clinical, with conversion to MS in a cohort of people with a radiologically isolated syndrome (RIS).

Methods: This multicentric observational study analyzed patients in the RIS Consortium cohort during the pandemic between January 2020 and December 2022. We compared the occurrence of disease activity in patients according to their vaccination status. The same analysis was conducted by comparing patients' history of COVID-19 infection.

Results: No difference was found concerning clinical conversion to MS in the vaccinated versus unvaccinated group (6.7% vs 8.5%, $p > 0.9$). The rate of disease activity was not statistically different (13.6% and 7.4%, respectively, $p = 0.54$). The clinical conversion rate to MS was not significantly different in patients with a documented COVID-19 infection versus non-infected patients.

Conclusion: Our study suggests that COVID-19 infection or immunization in RIS individuals does not increase the risk of disease activity. Our results support that COVID-19 vaccination can be safely proposed and repeated for these subjects.

Keywords: Radiologically isolated syndrome, COVID-19, vaccines

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Introduction

The radiologically isolated syndrome (RIS) was defined in 2009 by Okuda et al.¹ as incidental magnetic resonance imaging (MRI) abnormalities suggestive of multiple sclerosis (MS). These white matter lesions identified on MRI are discovered incidentally and fulfill the criteria for dissemination in space (DIS), with no associated neurological clinical event suggestive of the central nervous system (CNS) demyelinating disease. Postmortem studies estimate RIS prevalence between 0.06% and 0.7%.² Overall,

the cumulative incidence of RIS is approximately 0.1%.³ In a multicentric study directed by the RIS Consortium (RISC), the estimated 5- and 10-year risk of developing a first clinical event was 34% and 51.2%, respectively.^{4,5} These studies identified significant predictors associated with a higher risk of conversion to MS, such as young age, male sex, cerebrospinal fluid (CSF)-restricted oligoclonal bands (OCBs), and spinal cord or infratentorial lesions. The impact of MS-approved disease-modifying therapies (DMTs) within this group recently demonstrated an

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80% relative risk reduction of dimethyl fumarate compared to placebo.⁶ Another multicentric study investigating the efficacy of teriflunomide in delaying the time to MS conversion is pending.⁷

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus.⁸ Infections can lead to severe pulmonary affection, sometimes requiring oxygen therapy or other respiratory assistance. Some patients can experience long-term effects of their conditions, with symptoms persisting or appearing many months after the typical recovery. Several vaccines have been designed, including mRNA (Pfizer/BioNTech, Moderna), adenovirus vector vaccines (AstraZeneca, Janssen), inactivated virus vaccines (Sinovac), and recombinant protein vaccines (Sanofi). The vaccination campaign started in January 2021 in France, Turkey, and the United States, being a cornerstone to slow down the pandemic.

The safety of these vaccines in patients with demyelinating diseases has been debated. Concerns about the potential risk of triggering disease activity have been raised, leading to global vaccination hesitancy in this population. Several societies,^{9–12} including the French MS society (Société Francophone de la Sclérose en Plaques (SFSEP)), recently published recommendations concerning vaccinations in patients with MS, concluding that the general use of vaccines was safe and efficient.¹³ The American Academy of Neurology (AAN) and theECTRIMS/EAN experts concluded insufficient data to support or refute an association between the development of MS and vaccination. They recommended that people with MS receive vaccines according to standard vaccine guidelines.¹⁴ Regarding COVID-19, no specific warning has been identified, and vaccination of patients with inflammatory diseases of the CNS has thus been recommended.^{15–19}

To date, no study is available about the impact of immunization on the RIS.

The primary objective was to evaluate if COVID-19 vaccination could increase the risk of clinical conversion to MS in RIS. The secondary purpose was to assess if COVID-19 vaccination or infection increases the risk of evidence of disease activity (EDA) in the preclinical stage of MS.

Methods

Patients

This multicentric observational study is based on the RISC and the SFSEP (French MS society) cohort

(France, the United States, and Turkey). This cohort is registered on the Clinical Trials platform (NCT05388331), in which individuals identified as presenting with an RIS according to the 2009 diagnostic criteria¹ are included.

Baseline demographical, biological, and MRI data are collected. A standardized, prospective follow-up every year, including screening for the occurrence of a first clinical attack associated with CNS demyelination and systematic MRI follow-up, is also performed.

During the COVID-19 vaccination campaign, additional data were collected using a standardized form in each participating center, including the number and administered vaccines and history of documented COVID-19 infection (based on the positivity of an antigenic or PCR nasopharyngeal test). Subjects were excluded if (1) vaccination records were missing or incomplete, (2) if a first clinical event occurred before the COVID-19 vaccination, and (3) if any other vaccine was administered during the study period. Data regarding COVID-19 were collected between January 2021 and December 2022.

Outcome measures

The clinical conversion was defined as a neurological event consistent with MS relapse, lasting > 24 hours without fever or other acute illness. Specialists in neuroimmunology systematically confirmed all clinical events.

EDA was described as a new or enlarged T2-weighted hyperintense lesion or gadolinium-enhancing lesion on a follow-up MRI performed after vaccination.

Statistical analysis

We described the demographical features of the cohort and compared patient groups according to the vaccination status and history of COVID-19 infection.

Complete vaccination (CV) was defined as administering two doses of an mRNA (Pfizer/BioNTech, Moderna) or AstraZeneca vaccine, administration of one dose of Janssen vaccine, or administration of one dose of any vaccine in patients with a history of COVID-19 infection before the onset of vaccination. Other patients were defined as incompletely vaccinated if they received at least one dose of the vaccine without fulfilling the CV definition and unvaccinated (UV) if they did not receive any dose of any vaccine.

We compared the conversion rate to a first event related to CNS demyelination and EDA in both groups of patients.

Means with standard deviations (SD) were calculated to describe the numerical demographical features of the population. Categorical variables were reported as counts and percentages, and continuous variables were declared as median and quartile ranges. A comparison of quantitative measures between patient groups was assessed using the Mann–Whitney U test. Qualitative measures were compared between patient groups using the chi-square test. The p-values less than 0.05 were considered statistically significant. Data analysis was performed using EasyMedStat and R software (R Core Team, 2014. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org>).

Sample size

Our study was an exploratory study that aimed to collect data about COVID vaccination and SARS-Cov-2 infections in the entire RISC cohort. Thus, we did not perform a sample size calculation.

Ethical statement

This study was declared on clinical trials (NCT05387395). It complied with reference methodology MR-004 (*Commission Nationale de l'Informatique et des Libertés*) and was registered on the French Health Data Hub (Registration ID: F20220531152854). Personal data have been collected and processed by the laws and regulations in France and local laws in force in Turkey and in the United States.

This study was approved by the following regulatory authorities and ethics committees: Committee on Human Research (University of California, San Francisco, San Francisco, California, USA), Mayo Clinic Institutional Review Board (Mayo Clinic, Rochester, Minnesota, USA), University of Texas Southwestern at Dallas (Dallas, Texas, USA), Istanbul University Cerrahpasa School of Medicine Ethical Committee for Clinical Research and Studies (Istanbul, Turkey), and the Comité de Protection des Personnes (Hôpital Pasteur2, Nice, France). Written informed consent was acquired from all study subjects.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Results

Data regarding COVID-19 vaccination and infection were collected for 346 RIS subjects from 17 centers. Among the whole population, 70 patients (20.2%) were not vaccinated and 269 patients (77.7%) had a CV. The most frequently administrated vaccine was Pfizer/BioNTech (77%), followed by Sinovac (12.5%), Moderna (6.1%), AstraZeneca (3.9%), and Janssen (0.5%). Seven patients (2.1%) were incompletely vaccinated and were excluded from the analysis (cf. Figure 1).

Consequently, the study population included 339 patients. The demographic characteristics are detailed in Table 1. There was no significant difference between the vaccinated and unvaccinated groups concerning demographical characteristics, notably regarding known risk factors of conversion to MS, that is, age, sex, lesions' location, and the presence of OCB in the CSF.

In our cohort, 84 patients (27.8%) had a history of COVID infection, among which 27 were completely vaccinated. The demographic and radiological characteristics of patients with or without a history of COVID-19 disease were comparable.

Primary outcome: vaccination and clinical conversion to MS

Among the population, 38 subjects presented a first clinical event before the first vaccination jab and were excluded from the primary outcome analysis. In the analyzed cohort ($n=312$), the first clinical event occurred in 18 subjects (6.7%) of the vaccinated group and 6 subjects (8.5%) of the unvaccinated group. No significant difference was found between these two parameters ($p > 0.9$). When clinical conversion occurred after vaccination, the mean delay to the first clinical event was 172 days, ranging from 5 to 427 days after the first vaccination.

Secondary outcomes

Brain MRI follow-up data were available for 189 RIS subjects, 162 in the CV and 27 in the IV groups. The demographical data were not statistically different between patients with and without follow-up MRI regarding age, gender, and baseline RIS characteristics (MRI and biological data).

EDA occurred in 22 patients (13.6%) in the vaccinated group and in 2 (7.4%) in the unvaccinated group. The observed difference was not statistically significant ($p=0.54$).

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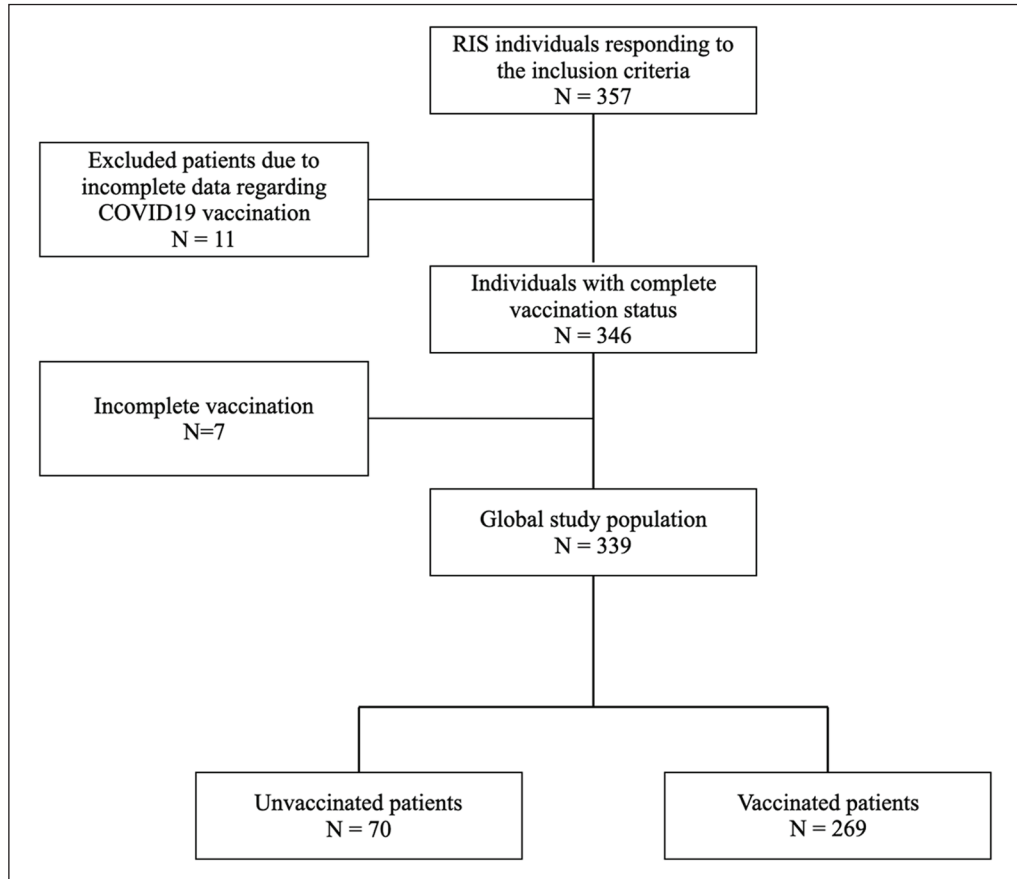


Figure 1. Study flowchart.

Table 1. Demographic characteristics and ancillary findings of CV and incomplete or absent vaccination (IV), and the COVID-19 infected population and no infected.

	Global population (n=339)	CV N=269	IV N=70	p	History of COVID-19 N=84	No history of COVID-19 N=218	p
Females, %	72.8	75.5	64.9	0.09	76.2	71.1	0.46
Age (years, <i>M</i> ± <i>SD</i>)	38.4 ± 12.4	38.7 ± 12.6	37 ± 12	0.25	37.1 ± 12.9	38.5 ± 12.2	0.27
Caucasian, %	90.1	90.2	88.3	0.59	93.9	88.9	0.93
Initial MRI							
Spinal cord lesion, %	29.7	20.5	28.5	0.18	19	20.1	0.31
At least one gadolinium-enhancing lesion, %	15.2	16.4	10.5	0.3	19.5	13.7	0.26
At least one infratentorial lesion, %	48	48.1	47.1	0.93	63.6	53	0.51
CSF OCBs, %	63	65.9	57.1	0.55	83.3	70.3	0.51

Impact of COVID-19 infection on RIS course
 Among 84 RIS subjects who developed a documented COVID-19 infection, conversion to MS occurred before the onset of infection in 12 individuals excluded from this analysis. In the analyzed population, the first clinical event occurred in 8 patients

(12.1%) with a history of COVID-19 infection versus 27 patients (13.5%) without COVID-19 infection. No significant difference was demonstrated ($p > 0.999$).
 MRI follow-up data were available in 62/72 (86.1%) subjects in the infected group and 119/218 (54.5%) in

the non-infected group. EDA occurred in 10 patients (16.1%) and 9 patients (7.6%), respectively, with a non-significant difference ($p=0.123$)

Discussion

We conducted a prospective study to assess whether COVID-19 vaccines for preventing SARS-Cov-2 infection could impact the risk of conversion to MS in RIS subjects. Our results showed that the COVID-19 infection and vaccination did not lead to a substantial risk increase in clinical conversion or EDA.

This is the first study investigating the safety of COVID-19 vaccines regarding disease activity in RIS subjects. Several studies explored disease activity after COVID-19 vaccination in MS patients.^{20–28} Most results highlighted that vaccination was not associated with a higher risk of relapse. A multicentric observational study conducted in Italy²⁹ involving 324 patients with MS showed that Pfizer/BioNTech vaccine did not increase the short-term risk of acute exacerbations 2 months post-exposure. An Israelite study²⁴ assessed vaccination safety in adult MS patients. Vaccinated MS patients did not show increased clinical disease activity over a median follow-up of 20–38 days. The rate of patients with acute relapses (2.1% after the first dose and 1.6% after the second dose) was like the rate in unvaccinated patients evaluated in the corresponding period in 2017, 2018, 2019, and 2020. Finally, a recent meta-analysis of 19 studies gathering more than 14,000 MS patients concluded that COVID-19 vaccination was not associated with an increased risk of disease activity.²⁸

Conversely, two reports^{20,25,27} and one case series²² of 16 patients described MS relapses shortly after COVID-19 vaccination. Still, the timing between the vaccination and relapse occurrence was often very short, raising the question of a true causality between the two events. One publication reports the clinical experience of a young woman with relapsing–remitting MS (RRMS) treated with rituximab. However, 3 months after the last infusion and 2 days after her first vaccination by Sputnik V, she presented a relapse associated with new lesions on brain MRI.²⁰ No patient within our cohort received the Sputnik V vaccination, and only a few cases were vaccinated with adenovirus vector vaccines.

In addition, one case reported relapse in a young woman diagnosed with RRMS in 2016 who received two courses of cladribine in 2018 and 2019 without any other disease-modifying treatment later. The relapse occurred in April 2021, 2 days after her first

injection of the Pfizer COVID-19 vaccine. MRI showed three new gadolinium-enhancing lesions compared to a previous scan performed 6 months before.²² Nistri *et al.* reported data from 16 patients managed in four Italian MS centers referred after COVID-19 vaccination. The most frequently administered vaccine was Pfizer/BioNTech. Three patients received a new diagnosis of MS after the COVID-19 vaccination, 3–8 days after their first dose. Among other patients, nine were on disease-modifying treatment and presented a relapse between 1 and 21 days after vaccination. All patients had EDA on MRI to support the relapse diagnosis, but the timing of the MRI after symptom onset was very heterogeneous (3–50 days). This latter suggested a temporal association between disease activity and COVID-19 vaccination.²²

Finally, a recent prospective study hypothesized that the AstraZeneca vaccine could be associated with a higher risk of developing myelin oligodendrocyte glycoprotein antibody-associated disease.³⁰ Still, no relationship with MS onset was recorded. Moreover, only 11 individuals in our study population received this vaccine (3.9%)

In France, the Periodic Safety Update Reports (PSUR), which evaluates the risk–benefit balance of a medicinal product at defined time points after authorization, did not publish concerns about MS relapse after COVID vaccination.³¹

Regarding vaccination in general, the evidence of an association between vaccination and MS activity has already been debated.^{10,32–35} Several societies published recommendations about vaccinations in MS populations. The French MS society SFSEP¹³ did not identify an increased risk of MS or relapse after vaccination and recommended comprehensive vaccination in MS patients. The AAN¹⁴ concluded that data are insufficient to support or refute an association between the development of MS or the occurrence of relapse and history of vaccination. Thus, AAN experts recommended that people with MS receive vaccines according to the standard guidelines.

In our analysis, neither COVID-19 vaccination nor COVID-19 infections were associated with a higher risk of EDA, even if MRI data were unavailable for the whole cohort. We did not find any other data regarding systematic radiological assessment of MS activity after COVID-19 vaccination or infection, except for the few previously cited case reports or series for which MRI data were available in the setting of a relapse. Further studies based on regular

MRI follow-ups on larger cohorts of MS patients could support our results.

Our cohort did not show an increased risk of conversion to MS after COVID-19 infection.

To our knowledge, the correlation between infections and RIS conversion to MS has never been studied. In addition, the question of the potential role of conditions in triggering disease activity in MS has been raised for a long time. The French MS society and theECTRIMS^{31–33,36} recently concluded in a set of recommendations about infections and MS that the role of viral, bacterial, or fungal infections in increasing the risk of relapse in MS was not endorsed because of the limited size, retrospective nature, and the lack of MRI information in the available studies. Consequently, the authors stated that infection in MS patients, in general, could lead to a transient worsening of disability in case of fever but were not associated with an increased risk of relapse or permanent worsening of disability. More specifically, a recent publication raised the hypothesis that MS could be triggered by COVID-19 infection in relationship with molecular mimicry between SARS-CoV-2 nucleocapsid and myelin proteolipid protein.³⁷ However, to date, no clinical data support this hypothesis.

Our study also has several limitations. The experimental design, without sample size calculation, can raise the hypothesis of a lack of study power can be raised. In addition, MRI data were only collected for part of the cohort, mainly because of the lockdowns related to the pandemic, which did not allow patients to perform their annual exams. Moreover, the timing between vaccination and MRI needed to be standardized. However, our findings suggest that the COVID-19 vaccination is safe in subjects with RIS and should be proposed without concern regarding a potential risk of disease evolution.

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: M.C. has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Ad Scientiam, Biogen, Merck, Sanofi-Genzyme, Roche, Celgene/Bristol Myers Squibb (BMS), Alexion, Horizon Therapeutics, none related to this study. O.T.R. has nothing to disclose. A.S. reported serving on the steering committee for the ARISE and Teriflunomide in Radiologically Isolated Syndrome (TERIS) studies. D.T.O. received personal


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