Impact of mass vaccination on SARS-CoV-2 infections among the total multiple sclerosis population receiving immunomodulatory disease-modifying therapies in England

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Abstract

This study aimed to understand changes in the risk of SARS-CoV-2 infection among all people with multiple sclerosis (MS) receiving immunomodulatory disease-modifying therapies (DMTs) in England, compared to the general population, following mass vaccination. Longitudinal data collected by the National Health Service (NHS) England on all MS DMT prescriptions and the UK Health Security Agency on all registered SARS-CoV-2 test results were analysed. The incidence rate ratio of SARS-CoV-2 infection among people with MS taking DMTs compared to the general population was calculated before (November 2020-January 2021) and after (July-August 2021) mass vaccination. Risk of SARS-CoV-2 infection among people on ocrelizumab or fingolimod compared to the general population increased following liberalisation of COVID-19 restrictions (during March-July 2021) despite mass vaccination. No changes were found with other DMTs. These findings converge with the impaired immune response to vaccines observed with ocrelizumab and fingolimod.

Introduction

The launch of COVID-19 vaccines was inarguably a game changer amid worldwide efforts to control the pandemic. While real-world data in the general population continue to show that vaccination is effective in preventing SARS-CoV-2 infections (www.gov.uk/government/publications/covid-19-vaccine-surveillance-report), it is still unclear whether vaccination offers the same level of protection for people receiving immunomodulatory medications. It is estimated that 2.8% of adults in the United States are on immunosuppressive treatments,1 and many people receive other immunomodulatory medications. Immunological studies are reporting their results on antibody- and cell-mediated immune responses to SARS-CoV-2 vaccines among people under immunosuppressive therapies,1–4 but they do not include findings on the effectiveness of vaccines in preventing infections in these populations which is a main purpose of vaccination (www.ecdc.europa.eu/en/publications-data/objectives-vaccination-strategies-against-covid-19). It is important that monitoring the population effect of SARS-CoV-2 vaccination is inclusive of people on immunomodulatory treatments,5 especially as COVID-19 restrictions, such as physical distancing or wearing face coverings, are being relaxed.

Many people with multiple sclerosis (MS), an autoimmune disorder of the central nervous system, are treated using immunomodulatory disease-modifying therapies (DMTs) and are understandably concerned about the protection SARS-CoV-2 vaccination offers them.

The aim of the present study was to understand the impact of mass SARS-CoV-2 vaccination on the entire population of people with MS taking DMTs in England in preventing SARS-CoV-2 (symptomatic and asymptomatic) infections.

National Health Service (NHS) England and NHS Improvement (NHSE/I) acquire monthly prescribing and dispensing data on all NHSE/I commissioned MS DMTs in England (www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04). UK Health Security Agency (UKHSA; previously known as Public Health England) has continuously collected data on all registered SARS-CoV-2 test results, including polymerase chain reaction (PCR) and rapid antigen tests, during the COVID-19 pandemic (coronavirus.data.gov.uk). The datasets from NHSE/I and UKHSA were merged to estimate the monthly incidence rate of SARS-CoV-2 infections from March 2020 to August 2021 in the entire population of people with MS taking different DMTs in England. Publicly available data were used for estimation of the monthly incidence rate of SARS-CoV-2 infections in the general population (20-years-old or above) in England during the same period (coronavirus.data.gov.uk/details/cases?areaType=nation&areaName=England) (www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2020). In England, mass SARS-CoV-2 vaccination started in December 2020 (www.england.nhs.uk/2020/12/landmark-moment-as-first-nhs-patient-receives-covid-19-vaccination) and national restrictions imposed by COVID-19 were gradually lifted during March to July 2021 (www.gov.uk/government/publications/covid-19-response-spring-2021/covid-19-response-spring-2021-summary). The incidence rate ratio (IRR) of SARS-CoV-2 infection in people with MS taking individual DMTs compared to the general population was calculated during two waves of the COVID-19 pandemic in England: (1) three months around the time of mass SARS-CoV-2 vaccination initiation (i.e., November 2020, December 2020, and January 2021) referred to as the ‘pre-vaccination’ period, and (2) three months following the roll-out of mass vaccination (i.e., June, July, and August 2021) referred to as the ‘post-vaccination’ period.

Results

A mean (standard deviation) of 41,208 (4,301) people with MS received a DMT in England during each month from March 2020 to August 2021. A total of 3,524 people with MS had a positive SARS-CoV-2 PCR or rapid antigen test (i.e., SARS-CoV-2 infection) during this period. The incidence rate of SARS-CoV-2 infection among people on ocrelizumab or fingolimod compared to the general population increased following the lifting of COVID-19 restrictions despite mass vaccination and a reduction in infections among the general population.

The IRR (95% confidence interval [CI]) of SARS-CoV-2 infection for people on ocrelizumab compared to the general population significantly increased from 1.13 (0.97 – 1.31) during the pre-vaccination period to 1.79 (1.57 – 2.03) during the post-vaccination period (Figure 2). The IRR (95% CI) of SARS-CoV-2 infection for people on fingolimod compared to the general population also significantly increased from 0.87 (0.73 – 1.02) to 1.40 (1.20 – 1.63) during the same periods (Figure 2). There were no significant changes in the IRR for people on other MS DMTs compared to the general population (Supplementary Data 2 and Supplementary Data 3).

Discussion

This study presents the incidence of SARS-CoV-2 infection for the entire population of people with MS receiving a DMT in England and compares their risk of infection to the general population during two waves of the COVID-19 pandemic—before implementation of mass SARS-CoV-2 vaccination and when at...
least 74% and 56% of the adult population in England had received their first and second dose of vaccine, respectively (coronavirus.data.gov.uk/details/vaccinations?areaType=nation&areaName=England). To our knowledge, this is the first study to report changes in the incidence of SARS-CoV-2 infection in relation to mass vaccination in a population under immunomodulatory therapies. Although individual-level data on SARS-CoV-2 vaccination was not available at the time of the study, the MS population were expected to have a similar pattern of vaccination to the general population as they had a high willingness to receive the vaccine, or may have been vaccinated earlier (for example, people with severe neurological disabilities or those taking alemtuzumab or ocrelizumab) (www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a). The study used SARS-CoV-2 test results to estimate the incidence rate of infection, which includes both symptomatic and asymptomatic infections.

Recognising these limitations, the findings of this study show a substantial increase in the risk of SARS-CoV-2 infection among people on ocrelizumab or fingolimod compared to the general population following liberalisation of COVID-19 restrictions and despite mass SARS-CoV-2 vaccination. There were no obvious changes in the risk of SARS-CoV-2 infection among people taking other MS DMTs.

Ocrelizumab is an anti-CD20 monoclonal antibody that causes B-cell depletion. People on ocrelizumab or rituximab, another anti-CD20 therapy used for treatment of MS in some countries, show reduced antibody and memory B-cell responses to SARS-CoV-2 vaccines. Nevertheless, a few studies reported that they can mount a T-cell response suggesting that vaccination may offer some protection against SARS-CoV-2 to people on B-cell depleting therapies. It was unknown, however, how this interplay between humoral and cellular immune responses translated into protecting people on anti-CD20 medications from infection. Fingolimod is a sphingosine-1-phosphate receptor modulator which inhibits lymphocyte egress from lymphoid tissues into the circulation. This MS DMT also seems to prevent the production of antibodies in response to SARS-CoV-2 vaccination.

So far, assumptions about the impact of MS DMTs on the effectiveness of SARS-CoV-2 vaccines are mostly based on experiences with previous vaccinations and immunological studies rather than population-based studies. Although a few studies have suggested that antibody levels serve as a correlate of protection from SARS-CoV-2 infection, it is undecided whether these antibodies are the main executors of this protection or they are simply biomarkers of the orchestrated function of the triggered immune system against the virus. Cohort studies of people taking immunomodulatory drugs are required to assess the effectiveness of SARS-CoV-2 vaccines in these populations. A few such studies have already been set up, but it will be a while before they are concluded. The findings of our study suggest that the humoral immune response to vaccines, which is suppressed by ocrelizumab and fingolimod and preserved by other MS DMTs, may be mainly responsible for the protection provided against SARS-CoV-2.

We noted also that the risk of SARS-CoV-2 infection associated with beta-interferons was lower than the general population, both pre- and post-vaccination, which is not unexpected given their antiviral effects.

The effectiveness of SARS-CoV-2 vaccination in preventing symptomatic infections and severe disease among people taking MS DMT is yet to be determined. The timing of vaccination in relation to administration of some MS DMTs, such as alemtuzumab, cladribine, and ocrelizumab, can affect the development of an immune response to the vaccine depending on whether or not repopulation of the immune cells has occurred. This consideration was not applied in the present study because individual-level vaccination data were not available.

The findings of this study suggest that SARS-CoV-2 vaccines offer minimal, if any, protection against infection to people taking ocrelizumab or fingolimod. Large-scale population studies using individual-level data on SARS-CoV-2 vaccination status, antibody levels, incidence of infection along with severity of disease are required to establish the benefits of current vaccination programmes that are offering third dose vaccines to people with drug-induced immunosuppression.

Methods

This observational study is a retrospective analysis of longitudinally collected data by NHSE/I and UK Health Security Agency (previously known as Public Health England) on SARS-CoV-2 test results for all people with MS taking a DMT in England.

Population data

NHSE/I acquire monthly prescribing and dispensing data on all NHSE/I commissioned MS DMTs in England (www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04). The total number of people with MS on any given DMT during each month was estimated based on their last DMT prescription since the start of January 2019 before and including the last day of each month from March 2020 to August 2021. The total population of England was collected from public data provided by the Office for National Statistics (www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2020). In the absence of individual-level data, the total population of adults aged 20 years or above was used in the analysis as over 98% of the MS population are estimated to be adults (www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms).

SARS-CoV-2 infection data

UKHSA has been collecting data on all registered SARS-CoV-2 test results, including PCR and rapid antigen tests, from the start of the COVID-19 pandemic which is publicly available for the general population (coronavirus.data.gov.uk). The datasets of NHSE/I and UKHSA were merged to identify all people with MS taking a DMT who had tested positive for SARS-CoV-2 during each month from March 2020 to August 2021. For any person with MS who had tested positive for SARS-CoV-2, their last prescribed DMT before the date of the positive test was used to determine the MS DMT they were taking when they were counted as a case of SARS-CoV-2 infection.
People who met any of the following criteria were included as cases of SARS-CoV-2 infection: 1) a positive PCR test; 2) a positive rapid antigen test confirmed by a positive PCR test taken within 72 hours; 3) a positive rapid antigen test when a PCR test was not taken within 72 hours (89.8%, 7.4%, and 2.8% of cases in the general population by the end of August 2021, respectively) (coronavirus.data.gov.uk). People with a positive rapid antigen test but a negative PCR test taken within 72 hours were not considered as cases of SARS-CoV-2 infection. People with more than one positive test for SARS-CoV-2 were counted once and the date of their first positive test was used.

People with MS who could not be linked between the NHSE/I and UKHSA datasets were excluded from the analysis. If a prescribing date had not been provided in the NHSE/I dataset, the date in which data was submitted to NHSE/I was used.

**Statistical analysis**

The incidence rate of SARS-CoV-2 infection was calculated for the general population and for people with MS on any given DMT as the number of cases divided by the total number within the relevant population.

The IRR was calculated as a point estimate of the incidence rate of SARS-CoV-2 infection among people taking each MS DMT divided by the incidence rate among the general population. The 95% CI was estimated using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). The IRR and 95% CI were calculated for each month during the study period as well as during two waves of the COVID-19 pandemic: (1) a three-month period around the start time of mass SARS-CoV-2 vaccination in England (November 2020, December 2020, and January 2021) referred to as ‘pre-vaccination’ period, and (2) a three-month period following mass vaccination (June, July, and August 2021) referred to as ‘post-vaccination’ period.

**Declarations**

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**Author Contributions**

NE conceived the study with support from AC, DB, AG, and WR. NE and AG planned the study with support from all authors. SP prepared the data with support from DB, AG, and NE. GRL analysed the data with support from AG and NE. AG prepared the figures with support from NE, GRL and SP. AG wrote the original draft of the manuscript with NE, and all authors reviewed and edited the manuscript.

**Competing Interests statement**

Afagh Garjani has received research support from the United Kingdom Multiple Sclerosis Society, speaker honorarium and travel support from the Multiple Sclerosis Academy, and travel support from Novartis and Merck.

Sameer Patel declares no competing interests.

Dhiren Bharkhada declares no competing interests.

Waqar Rashid declares no competing interests.

Alasdair Coles declares no competing interests.

Graham R Law declares no competing interests.

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**References**

1. Kearns, P., *et al.* Examining the Immunological Effects of COVID-19 Vaccination in Patients with Conditions Potentially Leading to Diminished Immune Response Capacity–The OCTAVE Trial. (2021).

2. Apostolidis, S.A., *et al.* Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. *Nature Medicine*, 1–12 (2021).

3. Mahil, S.K., *et al.* The effect of methotrexate and targeted immunosuppression on humoral and cellular immune responses to the COVID-19 vaccine BNT162b2: a cohort study. *The Lancet Rheumatology* 3, e627-e637 (2021).

4. Moor, M.B., *et al.* Humoral and cellular responses to mRNA vaccines against SARS-CoV-2 in patients with a history of CD20 B-cell-depleting therapy (RituxiVac): an investigator-initiated, single-centre, open-label study. *The Lancet Rheumatology* (2021).

5. Pritchard, E., *et al.* Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom. *Nature Medicine*, 1–9 (2021).

6. Huang, Y., *et al.* Willingness to receive a COVID-19 vaccine in people with multiple sclerosis–UK MS Register survey. *Multiple sclerosis and related disorders* 55, 103175 (2021).
7. Lee, D.S., Rojas, O.L. & Gommerman, J.L. B cell depletion therapies in autoimmune disease: advances and mechanistic insights. *Nature Reviews Drug Discovery* **20**, 179–199 (2021).
8. Achiron, A., et al. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. *Therapeutic Advances in Neurological Disorders* **14**, 17562864211012835 (2021).
9. Sormani, M.P., et al. Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. *EBioMedicine*, 103581 (2021).
10. Brill, L., et al. Humoral and T-Cell Response to SARS-CoV-2 Vaccination in Patients With Multiple Sclerosis Treated With Ocrelizumab. *JAMA neurology* (2021).
11. Chiba, K. Discovery of fingolimod based on the chemical modification of a natural product from the fungus, Isaria sinclairii. *The Journal of Antibiotics* **73**, 666–678 (2020).
12. Cabreira, V., Abreu, P., Soares-dos-Reis, R., Guimarães, J. & Sá, M.J. Multiple Sclerosis, Disease-Modifying Therapies and COVID-19: A Systematic Review on Immune Response and Vaccination Recommendations. *Vaccines* **9**, 773 (2021).
13. Feng, S., et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nature Medicine*, 1–9 (2021).
14. Earle, K.A., et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* (2021).
15. Khoury, D.S., et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nature medicine*, 1–7 (2021).
16. Callaway, E. Scientists identify long-sought marker for COVID vaccine success. *Nature (Lond.)* (2021).
17. Loubet, P., et al. A French cohort for assessing COVID-19 vaccine responses in specific populations. *Nature Medicine* **27**, 1319–1321 (2021).
18. Dumitrescu, L., et al. Beta interferons as immunotherapy in multiple sclerosis: a new outlook on a classic drug during the COVID-19 pandemic. *QJM: An International Journal of Medicine* (2021).

**Figures**

![Figure 1](image-url)

**Figure 1**

Monthly incidence of SARS-CoV-2 infection from March 2020 to August 2021 among people with multiple sclerosis (MS) receiving disease-modifying therapies (DMTs) and the general population of 20-years-old or above in England. Data for individual DMTs (i.e., alemtuzumab, beta-interferons, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, ocrelizumab, and teriflunomide) are presented in separate graphs. The coloured line in each graph is the incidence rate of infection during each month per 100 people with MS taking each DMT, and the shaded areas are the 95% confidence intervals. The black line the incidence rate of infection during each month per 100 people aged 20 years or above in the general population. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both first and second doses) uptake during each month among the adult population in England.
Figure 2

Incidence rate ratio of SARS-CoV-2 infection among people with multiple sclerosis (MS) taking ocrelizumab (upper graph) and fingolimod (lower graph) compared to the general population aged 20 years or above in England during each month from September 2020 to August 2021. The coloured line in each graph is the incidence rate ratio and the shaded area is the 95% confidence interval. The black line demarcates the incidence rate ratio in the general population which is always one and serves as a reference line. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both first and second doses) uptake during each month among the adult population in England.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryData1.xlsx
- SupplementaryData2.xlsx
- SupplementaryData3.xlsx