



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Correspondence



Fingolimod impairs inactivated vaccine (CoronaVac)-induced antibody response to SARS-CoV-2 spike protein in persons with multiple sclerosis

ARTICLE INFO

Keywords

COVID-19
SARS-CoV-2
Vaccination
CoronaVac
Multiple sclerosis
Fingolimod

ABSTRACT

Background: : The impact of disease-modifying treatments on humoral response induced by inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines is understudied.

Methods: : We recruited 34 persons with multiple sclerosis (MS) under fingolimod treatment and 25 healthy individuals. Anti-SARS-CoV-2 spike IgG indices were measured by ELISA in sera of participants after CoronaVac vaccinations.

Results: : Persons with MS displayed significantly lower antibody levels and seropositivity prevalence. Persons with MS with longer fingolimod treatment durations displayed lower anti-SARS-CoV-2 indices.

Conclusion: : Our results support previous findings regarding humoral response impairing effect of fingolimod after vaccinations. Patients under fingolimod treatment may require closer monitoring for COVID-19.

Introduction

The ongoing Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has brought forward vaccination as a protective healthcare measure (Kwok, 2021; Hebbani et al., 2021). Although patients with autoimmune disorders, including multiple sclerosis (MS), are recommended to be vaccinated against COVID-19, the effect of disease-modifying therapies (DMTs) on the efficacy of vaccination is still under scrutiny. There is accumulating evidence of reduced humoral immunity to mRNA or viral vector-based COVID-19 vaccines among persons with MS (pwMS) under fingolimod or siponimod treatment (Achiron et al., 2021; Guerrieri et al., 2021; Krbot Skorić et al., 2021). Depending on the experience from inactivated flu vaccinations (Witman Tsur et al., 2021), pwMS may be recommended to receive inactivated SARS-CoV-2 vaccines, which are used in diverse geographical locations (Kwok, 2021; Hebbani et al., 2021). Nevertheless, little known about the impact of DMTs on the efficacy of inactivated SARS-CoV-2 vaccines. In this context, fingolimod is a particular concern due to previous observations regarding humoral and T-cell-specific immune response dampening actions of this DMT in MS (Achiron et al., 2021; Guerrieri et al., 2021; Kurtuncu et al., 2019; Tallantyre et al., 2022).

Materials and methods

Participants

In this prospective observational study, we recruited consecutive 34 persons with relapsing remitting MS (RRMS) under fingolimod treatment for 1–5 years. Fingolimod was the second DMT agent for all patients and initial DMTs were interferon-beta ($n = 23$) and glatiramer acetate ($n = 11$). All pwMS were in remission and had not received immunosuppressive medications other than fingolimod in the last 6

months or more. Patients with coexisting disorders or pregnancy or receiving additional medications were not included. A group of age/gender-matched and similarly vaccinated healthy individuals ($n = 25$) served as control (Table 1). None of the participants declared a clinical history suggestive of previous SARS-CoV-2 infection. The study was approved by the institutional review board and a written consent was obtained from all participants.

Sample collection and Elisa for antibodies

The CoronaVac vaccine (Sinovac Life Sciences, Beijing, China) contained 3 $\mu\text{g}/0.5\text{ mL}$ (equivalent to 600 SU per dose) of inactivated SARS-CoV-2. Two 0.5 mL intramuscular doses (deltoid muscle) were administered with a 30-day interval (day 0 and day 30). Sera were collected 28 days after both first (day 28) and second (day 58) vaccinations and kept at $-80\text{ }^\circ\text{C}$ freezer until analysis. Immunoassay for the detection of SARS-CoV-2 IgG antibodies in sera was performed using Euroimmun (Luebeck, Germany) quantitative ELISA kit, designed for detection of antibodies to spike protein of the SARS-CoV-2 virus. The assay was performed following the manufacturer's instructions and an index value higher than 1.1 was considered positive.

Results

None of the patients reported symptoms suggestive of SARS-CoV-2 infection during the study period. The only reported side effects by pwMS and healthy controls were transient fatigue and fever. The prevalence of anti-SARS-CoV-2 positive (seropositive) patients were respectively 3/35 (8.8%) and 4/25 (16%) in RRMS and healthy groups after the first vaccination ($p = 0.443$ by Fisher's exact test), whereas after the second vaccination seropositive prevalence respectively rose to 19/35 (56%) and 24/25 (96%) in RRMS and healthy groups ($p = 0.032$ by Fisher's exact test; Fig. 1). Antibody index values were comparable

<https://doi.org/10.1016/j.msard.2022.103524>

Received 13 December 2021; Received in revised form 26 December 2021; Accepted 9 January 2022

Available online 11 January 2022

2211-0348/© 2022 Elsevier B.V. All rights reserved.

Table 1

Demographic and clinical features of vaccinated multiple sclerosis (MS) patients and healthy controls (HC).

	MS (n = 34)	HC (n = 25)	p value
Age	37.8 ± 6.7 (24–47)	35.0 ± 7.5 (19–46)	0.317
Gender (women/men)	26/8	20/5	>0.999
Duration of MS (years)	6.4 ± 3.6 (3–12)	–	–
Total number of attacks	5.0 ± 1.8 (2–8)	–	–
EDSS	2.6 ± 0.8 (1.5–4.0)	–	–
Duration of fingolimod treatment (years)	1.7 ± 1.4 (1–5)	–	–
White blood cells (x10 ³ /μl)*	7.0 ± 1.1 (5.2–8.8)	–	–
Lymphocytes (x10 ³ /μl)*	1.7 ± 0.7 (0.8–3.2)	–	–

Parametric variables are denoted as mean ± standard deviation (range).

EDSS, expanded disability status scale. Age and gender parameters were compared with Student's *t*-test and Fisher's exact test, respectively.

*Measured in blood sample obtained one day before first vaccination.

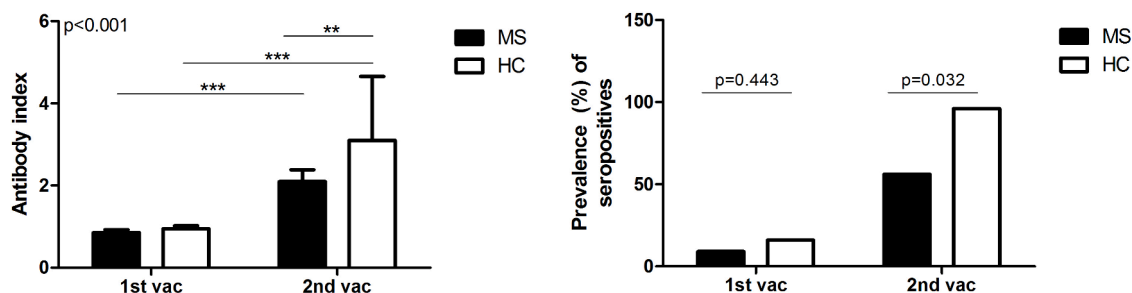


Fig. 1. Antibody index (left panel) and prevalence (right panel) of serum anti-SARS-CoV-2 spike protein antibody positivity of multiple sclerosis (MS) patients under fingolimod treatment and healthy controls (HC) vaccinated by CoronaVac (vac) twice (1st vac and 2nd vac). p value on the upper left corner of the left panel is obtained by ANOVA test. p values on the right panel were obtained by comparison of the respective groups by Fisher's exact test. **, $p < 0.01$ and ***, $p < 0.001$ by Tukey's post-hoc test. Vertical bars indicate standard errors.

after the first vaccination between RRMS (mean ± standard deviation; 0.8 ± 0.1 ; 0.2–2.3) and healthy control groups (0.9 ± 0.2 ; 0.1–2.8), whereas, after the second vaccination, antibody indices were significantly increased in both groups. At this point, healthy controls (3.1 ± 2.0 ; 0.2–7.8) displayed significantly higher index values than pwMS (2.3 ± 0.4 ; 0.3–5.9) (Fig. 1). Correlation analysis by Pearson test showed significant negative correlation between antibody index values (after 2nd vaccination) and fingolimod treatment durations of pwMS ($p = 0.032$; $R = -0.369$). No significant correlation could be found between index values versus age, disease duration, attack numbers, EDSS scores, peripheral blood white blood cell and lymphocyte counts.

Discussion

Overall, after both CoronaVac vaccinations, antibody index values and seropositivity rates were lower in pwMS under fingolimod treatment as compared to healthy controls. Almost half of pwMS failed to display a positive IgG response, whereas all but one of the healthy individuals showed positive IgG responses. Thus, our results show an impaired humoral response to CoronaVac vaccination in patients under fingolimod treatment. A second important finding was that pwMS with longer fingolimod treatment duration showed trends towards displaying lower anti-SARS-CoV-2 antibody levels. These findings are in agreement with previous reports showing decreased antibody responses in pwMS treated with a sphingosine 1-phosphate receptor modulator (fingolimod or siponimod) and vaccinated by mRNA-based, adenoviral vector-based and inactivated (BBIBP-CorV, Sinopharm) SARS-CoV-2 vaccines (Achiron et al., 2021; Guerrieri et al., 2021; Etemadifar et al., 2021; Krbot Skorić et al., 2021; Tallantyre et al., 2022). As a matter of fact, fingolimod has also been shown to impair antibody responses to other inactivated virus vaccines such as the influenza vaccine (Olberg et al., 2018).

Fingolimod is known to significantly reduce the numbers of peripheral blood B lymphocytes and T helper lymphocytes, both of which

are crucially involved in establishment of robust humoral responses against antigens (Kurtuncu et al., 2019). More importantly, fingolimod does not only decrease lymphocyte egress from lymphatic tissues but also impairs antigen presentation ability of dendritic cells (Zeng et al., 2012). Therefore, it is expectable that fingolimod interferes with the process of antibody production after vaccinations. pwMS under long-term fingolimod treatment may need to be closely monitored for insufficient immune response after vaccinations. Serial measurement of SARS-CoV-2 antibodies could be a useful method for this surveillance activity. A potential protection measure for patients under fingolimod treatment could be receiving early boosters in cases of insufficient protection and improvisation of more efficient vaccination strategies.

Ethics approval and consent to participate

Written informed consent was obtained from all participants and study was approved by the Institutional Review Board.

Disclosures

R. Türkoğlu, N. Baliç, T. Kızılay, R. Erol, E. Akbayır, V. Yılmaz and E. Tüzün report no disclosures. The authors have used no funds for this study to declare.

CRediT authorship contribution statement

Recai Türkoğlu: Conceptualization, Funding acquisition, Resources, Writing – review & editing. **Nesrin Baliç:** Data curation, Formal analysis, Investigation. **Tuğçe Kızılay:** Data curation, Formal analysis, Investigation, Methodology. **Ruziye Erol:** Data curation, Formal analysis, Investigation, Methodology. **Ece Akbayır:** Data curation, Formal analysis, Investigation, Methodology. **Vuslat Yılmaz:** Conceptualization, Funding acquisition, Resources, Writing – review & editing, Resources. **Erdem Tüzün:** Conceptualization, Funding acquisition,

Resources, Writing – review & editing, Resources.

Declarations of Competing Interest

The authors have no conflict of interest to declare.

References

- Achiron, A., Mandel, M., Dreyer-Alster, S., Harari, G., Magalashvili, D., Sonis, P., Dolev, M., Menascu, S., Flechter, S., Falb, R., Gurevich, M., 2021. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. *Ther Adv Neurol Disord* 14, 17562864211012835.
- Etemadifar, M., Sedaghat, N., Nouri, H., Lotfi, N., Chitsaz, A., Khorvash, R., Zolfaghari, H., Ghasemi Movaghar, A., Pourabbas, M., Salari, M., 2021. SARS-CoV-2 serology among people with multiple sclerosis on disease-modifying therapies after BBIBP-CorV (Sinopharm) inactivated virus vaccination: same story, different vaccine. *Mult Scler Relat Disord* 57, 103417.
- Guerrieri, S., Lazzarin, S., Zanetta, C., Nozzolillo, A., Filippi, M., Moiola, L., 2021. Serological response to SARS-CoV-2 vaccination in multiple sclerosis patients treated with fingolimod or ocrelizumab: an initial real-life experience. *J Neurol* 1–5.
- Hebbani, A.V., Pulakuntla, S., Pannuru, P., Aramgam, S., Badri, K.R., Reddy, V.D., 2021. COVID-19: comprehensive review on mutations and current vaccines. *Arch Microbiol* 204 (1), 8.
- Krbot Skorić, M., Rogić, D., Lapić, I., Šegulja, D., Habek, M., 2021. Humoral immune response to COVID-19 vaccines in people with secondary progressive multiple sclerosis treated with siponimod. *Mult Scler Relat Disord* 57, 103435.
- Kürtüncü, M., Yılmaz, V., Akçay, H.İ., Türkoğlu, R., Altunrende, B., Çınar, S.A., Ulusoy, C., Gündüz, T., İçöz, S., Kasap, M., Çalışkan, Z., Ötünç, G., Eraksoy, M., Tüzün, E., 2019. Impact of fingolimod on CD4+ T cell subset and cytokine profile of relapsing remitting multiple sclerosis patients. *J Neuroimmunol* 337, 577065.
- Kwok, H.F., 2021. Review of Covid-19 vaccine clinical trials - A puzzle with missing pieces. *Int J Biol Sci* 17 (6), 1461–1468.
- Olberg, H.K., Eide, G.E., Cox, R.J., Jul-Larsen, Å., Lartey, S.L., Vedeler, C.A., Myhr, K.M., 2018. Antibody response to seasonal influenza vaccination in patients with multiple sclerosis receiving immunomodulatory therapy. *Eur J Neurol* 25 (3), 527–534.
- Tallantyre, E.C., Vickaryous, N., Anderson, V., Asardag, A.N., Baker, D., Bestwick, J., Bramhall, K., Chance, R., Evangelou, N., George, K., Giovannoni, G., Godkin, A., Grant, L., Harding, K.E., Hibbert, A., Ingram, G., Jones, M., Kang, A.S., Loveless, S., Moat, S.J., Robertson, N.P., Schmierer, K., Scurr, M.J., Shah, S.N., Simmons, J., Upcott, M., Willis, M., Jolles, S., Dobson, R., 2022. COVID-19 Vaccine Response in People with Multiple Sclerosis. *Ann Neurol* 91 (1), 89–100.
- Witman Tsur, S., Adrian Zaher, E., Tsur, M., Kania, K., Kalinowska-Lyszczarz, A., 2021. Current Immunological and Clinical Perspective on Vaccinations in Multiple Sclerosis Patients: are They Safe after All? *Int J Mol Sci* 22 (8), 3859.
- Zeng, X., Wang, T., Zhu, C., Xing, X., Ye, Y., Lai, X., Song, B., Zeng, Y., 2012. Topographical and biological evidence revealed FTY720-mediated anergy-polarization of mouse bone marrow-derived dendritic cells in vitro. *PLoS ONE* 7 (5), e34830.

Recai Türkoğlu^a, Nesrin Baliç^a, Tuğçe Kızılay^a, Ruziye Erol^a,
Ece Akbayır^b, Vuşlat Yılmaz^b, Erdem Tüzün^{b,*}

^a Department of Neurology, Istanbul Haydarpaşa Numune Training and
Research Hospital, Istanbul, Turkey

^b Department of Neuroscience, Aziz Sancar Institute of Experimental
Medicine, Istanbul University, Istanbul, Turkey

* Corresponding author: Department of Neuroscience, Aziz Sancar
Institute of Experimental Medicine, Istanbul University, Istanbul,
Turkey, 34390.

E-mail address: drerdem@yahoo.com (E. Tüzün).