Siddiqui *et al.*
Egypt J Neurol Psychiatry Neurosurg (2021) 57:171
https://doi.org/10.1186/s41983-021-00428-8

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

LETTER TO THE EDITOR

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Adequate antibody response to BioNTech COVID vaccine in a multiple sclerosis patient treated with siponimod

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Keywords: COVID-19, Multiple sclerosis, Anti-COVID-19 vaccination, Sphingosine 1-phosphate receptor, Modulators, Disease-modifying therapy

To the editor,

We appreciated Mansoor and colleagues review entitled "COVID-19 pandemic and the risk of infection in multiple sclerosis patients on disease-modifying therapies: "what the bleep do we know?"" [1]. The authors examined available evidence guiding the management of multiple sclerosis (MS) patients during this pandemic, indicating that sphingosine 1-phosphate receptor modulators (S1PRM), including siponimod, could increase the risk of COVID-19 infection due to immunosuppression.

However, emerging data suggest that MS patients mount a humoral and cellular immune response even while receiving disease-modifying therapies (DMT) [2, 3]. For instance, retrospective data [2] from MS patients receiving S1PRM who completed two doses of anti-SARS-CoV-2 vaccination (either Pfizer or Moderna) showed positive anti-spike (S) protein antibody titers (Abbott or Roche SARS-CoV-2 IgG assay) determined forty-five and half days (average) after immunization. A wide range (16.1–80.4) of IgG index was observed. The incidence of COVID-19 infection, however, was not analyzed [2]. Surprisingly, the study suggested that based on "real-life experience", S1PRM could potentially hamper an effective humoral response to anti-COVID-19 vaccination in MS patients, which may unnecessarily discourage urgent immunization efforts.

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At the *Veterans Affairs Medical Center, Washington DC*, we have followed a 73-year-old man with active progressive MS (Expanded Disability Status Scale of 5.0) since 1995. He was initially treated in 1998 with *glatiramer acetate*, which was switched to siponimod (2 mg daily orally) since December 2019, achieving stabilization of neurocognitive decline. His absolute lymphocyte count was decreased (0.3 K/cmm, reference range 0.8–3.1 K/cmm) since July 2020. He received two doses of the BNT162b2 Pfizer vaccine (2/1/2021 and 2/22/2021), and his quarterly laboratory work-up (*complete cell blood counts, serum immunoglobulins, thyroid function, liver function, Chem 7, urine analysis, and fecal occult blood*) has been unremarkable, except for stable mild lymphopenia (0.3 K/cmm, 7/26/21) and mildly decreased IgM of 36 mg/dl (reference range 43–279 mg/dl). Additional immune evaluation (including lymphocyte subsets) was not performed. Anti-COVID-19 antibody testing was performed about 160 days after completion of vaccination (6/28/2021) and was positive for S (42.3 U/ml units, *Eclisys, Roche*) and negative for anti-nucleocapsid (0 U/ml, *Eclisys, Roche*) proteins, indicating adequate immune response to vaccination and absence of prior SARS-CoV-2 infection.

Universal consensus on anti-COVID-19 vaccination in MS patients treated with DMT is still emerging [2]. PubMed does not yield real-life data on the use of siponimod in MS patients exposed to COVID-19 or vaccination against it. Diminished immune response to non-COVID-19 vaccines have been reported after treatment with siponimod [4], which may be less

immunosuppressive than fingolimod (another S1RP inhibitor). Caution is necessary while using DMT in MS [1–3]. One must also consider that many studies are limited to static analysis of humoral responses without correlates with cell blood counts or neutralizing activity [2]. Further research is necessary to determine if DMT hamper appropriate immune responses, especially since the BNT162b2 vaccine also elicits T-cell immunity [5]. In summary, our experience suggests that siponimod may not significantly alter humoral immunity against COVID-19 vaccination, and may contribute to encourage vaccination against this pandemic in MS patients receiving DMT.

Abbreviations
COVID-19: Coronavirus disease 2019; MS: Multiple sclerosis; S1PRM: Sphingosine 1-phosphate receptor modulators; DMT: Disease-modifying therapies; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; Chem-7: Basic metabolic panel; BNT162b2: Pfizer-BioNTech COVID-19 vaccine.

Acknowledgements
Not applicable.

Authors' contributions
GS: design, literature search, discussion, first draft, critical comments. VN: design, literature search, discussion, critical comments, final approval. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
The data sets supporting the conclusion of this article are included within the article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors confirm that they have no competing interests.

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Received: 7 November 2021 Accepted: 30 November 2021
Published online: 14 December 2021

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