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.

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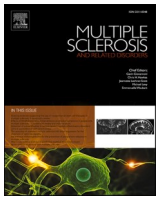

Commentary

How important are COVID-19 vaccine responses in patients with MS on disease-modifying therapies?

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Abbreviations
pwMS people with multiple sclerosis

The paper by Garjani and colleagues (Garjani et al., 2021) provides initial evidence that the risk of SARS-CoV-2 infection in patients with MS on ocrelizumab (anti-CD20) or fingolimod (S1P-modulator) is increased compared to the general population despite the mass COVID-19 vaccination in England. This pattern was not seen with other MS disease-modifying therapies.

In an Italian study of 1705 patients with MS who had been double vaccinated with one of the mRNA COVID-19 vaccines, there were 23 breakthrough COVID-19 infections, which were detected on average 108 days after the second dose (range, 18–230) (Sormani et al., 2021b). Nine were on ocrelizumab, one on rituximab, four on fingolimod, six on dimethyl-fumarate, one on teriflunomide, and two were untreated. Importantly only two patients, one on ocrelizumab and one on teriflunomide, required hospitalisation (Sormani et al., 2021b). In this study the probability of being infected was associated with SARS-CoV-2 anti-spike antibody levels measured after 4 weeks from the second vaccine dose; an antibody level of less than 660 U/mL was associated with a higher risk of infection (Sormani et al., 2021b).

These data are not surprising given that it has been confirmed that patients on ocrelizumab and fingolimod have blunted antibody responses to COVID-19 vaccines (Achiron et al., 2021a, 2021b; Apostolidis et al., 2021; Gadani et al., 2021; Sormani et al., 2021a; Tallantyre et al., 2022). What cannot be ascertained from these figures is whether cross-protective ancestral T-cell immunity to the Wuhan strain of SARS-CoV-2 (Gao et al., 2022), in the absence of humoral or antibody immunity, is sufficient to protect these patients from severe COVID-19, in particular serious infection with emerging immune escape variants such as Omicron (Sievers et al., 2022).

The Omicron strain and the likelihood of future immune escape variants challenge the widespread and rapidly adopted dogma to delay the introduction and/or further dosing of ocrelizumab (Baker et al., 2021) and fingolimod (personal communication Prof. Anat Achiron, Tel-Aviv University, Israel). The object of the latter is to permit sufficient peripheral B-cell reconstitution to facilitate an antibody response to the vaccine(s). Unless B-cell reconstitution is fully optimised, i.e. near normal, the level of neutralizing anti-spike SARS-CoV-2 antibody produced may not provide protective immunity against the Omicron variant (Achiron et al., 2021a). The potential downside to delayed dosing of ocrelizumab and fingolimod is whether their therapeutic efficacy is compromised. This is particularly relevant for fingolimod and other S1P modulators that are frequently associated with rebound inflammatory disease activity (Barry et al., 2019). This latter complication is less likely with ocrelizumab and other anti-CD20 therapies, which are associated with a treatment effect that extends beyond the period of B-cell reconstitution (Baker et al., 2020b; Rolfes et al., 2021; Sahi et al., 2021; Salzer et al., 2016).

Effective antiviral therapies for treating COVID-19 (García-Lledó et al., 2021) and the better management of severe COVID-19 ("Update to living WHO guideline on drugs for covid-19," 2021) have now emerged. They permit vulnerable people with MS (pwMS) whose vaccine responses are blunted, the opportunity to receive these treatments to prevent and/or manage severe COVID-19.

Based on these observations and the fact that the now dominant Omicron variant is less severe than the other strains (Abdullah et al., 2021) it is hard to justify a pause in DMT administration or delaying COVID-19 vaccination, be it the primary or booster vaccine doses. The maxim that some immunity is better than no immunity still holds and the general advice to pwMS would be to get vaccinated or boosted as soon as possible.

It is clear that the COVID-19 pandemic, and the emergence of effective COVID-19 vaccines, has taught us much about MS disease-modifying therapies and their impact on immune function (Baker et al., 2020a; Giovannoni et al., 2021). At some point, healthcare professionals and pwMS must accept that chronic continuous immunosuppression, which has transformed the prognosis of MS, comes at a cost, albeit relatively small, from infections, absent or suboptimal vaccine responses and secondary malignancies. There will always be a trade-off between efficacy and the short- and long-term safety of DMTs. As an MS community, we must generate robust evidence to allow patients and their healthcare professionals to make informed decisions about their care. National studies such as the ones highlighted here (Garjani et al., 2021; Sormani et al., 2021b) are helpful, but they need further revision

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to enable clinical decision making for individual patients.

References

Abdullah, F., Myers, J., Basu, D., Tintinger, G., Ueckermann, V., Mathebula, M., Ramlall, R., Spoor, S., de Villiers, T., Van der Walt, Z., Cloete, J., Soma-Pillay, P., Rheeder, P., Paruk, F., Engelbrecht, A., Lalloo, V., Myburg, M., Kistan, J., van Hougenhouck-Tulleken, W., Boswell, M.T., Gray, G., Welch, R., Blumberg, L., Jassat, W., 2021. Decreased severity of disease during the first global omicron variant covid-19 outbreak in a large hospital in Tshwane, South Africa. Int. J. Infect. Dis. 116, 38–42.

Achiron, A., Mandel, M., Dreyer-Alster, S., Harari, G., Dolev, M., Menascu, S., Magalashvili, D., Flechter, S., Givon, U., Guber, D., Sonis, P., Zilkha-Falb, R., Gurevich, M., 2021a. Humoral immune response in multiple sclerosis patients following PfizerBNT162b2 COVID19 vaccination: up to 6 months cross-sectional study. J. Neuroimmunol. 361, 577746.

Achiron, A., Mandel, M., Dreyer-Alster, S., Harari, G., Magalashvili, D., Sonis, P., Dolev, M., Menascu, S., Flechter, S., Falb, R., Gurevich, M., 2021b. 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.

Apostolidis, S.A., Kakara, M., Painter, M.M., Goel, R.R., Mathew, D., Lenzi, K., Rezk, A., Patterson, K.R., Espinoza, D.A., Kadri, J.C., Markowitz, D.M., E Markowitz, C., Mexhitaj, I., Jacobs, D., Babb, A., Betts, M.R., Prak, E.T.L., Weiskopf, D., Grifoni, A., Lundgreen, K.A., Gouma, S., Sette, A., Bates, P., Hensley, S.E., Greenplate, A.R., Wherry, E.J., Li, R., Bar-Or, A., 2021. Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. Nat. Med. 27, 1990–2001.

Baker, D., Amor, S., Kang, A.S., Schmierer, K., Giovannoni, G., 2020a. The underpinning biology relating to multiple sclerosis disease modifying treatments during the COVID-19 pandemic. Mult. Scler. Relat. Disord. 43, 102174.

Baker, D., MacDougall, A., Kang, A.S., Schmierer, K., Giovannoni, G., Dobson, R., 2021. Seroconversion following COVID-19 vaccination: can we optimize protective response in CD20-treated individuals? Clin. Exp. Immunol. https://doi.org/10.1093/cei/uxab015.

Baker, D., Pryce, G., James, L.K., Marta, M., Schmierer, K., 2020b. The ocrelizumab phase II extension trial suggests the potential to improve the risk: benefit balance in multiple sclerosis. Mult. Scler. Relat. Disord. 44, 102279.

Barry, B., Erwin, A.A., Stevens, J., Tornatore, C., 2019. Fingolimod rebound: a review of the clinical experience and management considerations. Neurol. Ther. 8, 241–250.

Gadani, S.P., Reyes-Mantilla, M., Jank, L., Harris, S., Douglas, M., Smith, M.D., Calabresi, P.A., Mowry, E.M., Fitzgerald, K.C., Bhargava, P., 2021. Discordant humoral and T cell immune responses to SARS-CoV-2 vaccination in people with multiple sclerosis on anti-CD20 therapy. EBioMedicine 73, 103636.

Gao, Y., Cai, C., Grifoni, A., Müller, T.R., Niessl, J., Olofsson, A., Humbert, M., Hansson, L., Österborg, A., Bergman, P., Chen, P., Olsson, A., Sandberg, J.K., Weiskopf, D., Price, D.A., Ljunggren, H.-G., Karlsson, A.C., Sette, A., Aleman, S., Buggert, M., 2022. Ancestral SARS-CoV-2-specific T cells cross-recognize the Omicron variant. Nat. Med. https://doi.org/10.1038/s41591-022-01700-x.

García-Lledó, A., Gómez-Pavón, J., González Del Castillo, J., Hernández-Sampelayo, T., Martín-Delgado, M.C., Martín Sánchez, F.J., Martínez-Sellés, M., Molero García, J. M., Moreno Guillén, S., Rodríguez-Artalejo, F.J., Ruiz-Galiana, J., Cantón, R., De Lucas Ramos, P., García-Botella, A., Bouza, E., 2021. Pharmacological treatment of COVID-19: an opinion paper. Rev. Esp. Quimioter. https://doi.org/10.37201/req/158.2021.

Garjani, A., Patel, S., Bharkhada, D., Rashid, W., Coles, A., Law, G.R., Evangelou, N., 2021. Impact of mass vaccination on SARS-CoV-2 infections among multiple sclerosis patients taking immunomodulatory disease-modifying therapies in England. Mult. Scler. Relat. Disord. 57, 103458.

Giovannoni, G., Hawkes, C.H., Lechner-Scott, J., Levy, M., Yeh, E.A., Baker, D., 2021. COVID-19 vaccines and multiple sclerosis disease-modifying therapies. Mult. Scler. Relat. Disord. 53, 103155.

Rolfes, L., Pawlitzki, M., Pfeuffer, S., Nelke, C., Lux, A., Pul, R., Kleinschnitz, C., Kleinschnitz, K., Rogall, R., Pape, K., Bittner, S., Zipp, F., Warnke, C., Goereci, Y., Schroeter, M., Ingwersen, J., Aktas, O., Klotz, L., Ruck, T., Wiendl, H., Meuth, S.G., 2021. Ocrelizumab extended interval dosing in multiple sclerosis in times of COVID-19. Neurol. Neuroimmunol. Neuroinflamm. 8 https://doi.org/10.1212/NXI.0000000000001035.

Sahi, N.K., Abidi, S.M.A., Salim, O., Abraham, R., Kalra, S., Al-Araji, A., 2021. Clinical impact of Ocrelizumab extended interval dosing during the COVID-19 pandemic and associations with CD19B-cell repopulation. Mult. Scler. Relat. Disord. 56, 103287.

Salzer, J., Svenningsson, R., Alping, P., Novakova, L., Björck, A., Fink, K., Islam-Jakobsson, P., Malmeström, C., Axelsson, M., Vågberg, M., Sundström, P., Lycke, J., Piehl, F., Svenningsson, A., 2016. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. Neurology 87, 2074–2081.

Sievers, B.L., Chakraborty, S., Xue, Y., Gelbart, T., Gonzalez, J.C., Cassidy, A.G., Golan, Y., Prahl, M., Gaw, S.L., Arunachalam, P.S., Blish, C.A., Boyd, S.D., Davis, M. M., Jagannathan, P., Nadeau, K.C., Pulendran, B., Singh, U., Scheuermann, R.H., Frieman, M.B., Vashee, S., Wang, T.T., Tan, G.S., 2022. Antibodies elicited by SARS-CoV-2 infection or mRNA vaccines have reduced neutralizing activity against Beta and Omicron pseudoviruses. Sci. Transl. Med. eabn7842.

Sormani, M.P., Inglese, M., Schiavetti, I., Carmisciano, L., Laroni, A., Lapucci, C., Da Rin, G., Serrati, C., Gandoglia, I., Tassinari, T., Perego, G., Brichetto, G., Gazzola, P., Mannironi, A., Stromillo, M.L., Cordioli, C., Landi, D., Clerico, M., Signoriello, E., Frau, J., Ferrò, M.T., Di Sapio, A., Pasquali, L., Ulivelli, M., Marinelli, F., Callari, G., Iodice, R., Liberatore, G., Caleri, F., Repice, A.M., Cordera, S., Battaglia, M.A., Salvetti, M., Franciotta, D., Uccelli, A., CovaXiMS study group on behalf of the Italian Covid-19 Alliance in MS, 2021a. Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. EBioMedicine 72, 103581.

Sormani, M.P., Schiavetti, I., Inglese, M., Carmisciano, L., Laroni, A., Lapucci, C., Visconti, V., Serrati, C., Gandoglia, I., Tassinari, T., Perego, G., Brichetto, G., Gazzola, P., Mannironi, A., Stromillo, M.L., Cordioli, C., Landi, D., Clerico, M., Signoriello, E., Frau, J., Ferrò, M.T., Sapio, A.D., Pasquali, L., Ulivelli, M., Marinelli, F., Manzino, M., Callari, G., Iodice, R., Liberatore, G., Caleri, F., Repice, A. M., Cordera, S., Battaglia, M.A., Salvetti, M., Franciotta, D., Uccelli, A., the CovaXiMS study group, 2021b. Breakthrough SARS-CoV-2 infections after COVID-19 mRNA vaccination in MS patients on disease modifying therapies. bioRxiv. https://doi.org/10.1101/2021.12.23.21268177.

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, 89–100.

Update to living WHO guideline on drugs for covid-19, 2021. BMJ 374, n2219.