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EDITORIAL

Vaccination responses in B-cell-depleted multiple sclerosis patients: The role of drug pharmacokinetics

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Early reports prior to availability of vaccinations show that treatment with anti-CD20 monoclonal antibodies (e.g., rituximab, ocrelizumab) in multiple sclerosis (MS) patients is associated with an increased risk of a more severe COVID-19 disease course [1, 2]. Consequently, there is much interest in SARS-CoV-2 vaccination-related immune dynamics of B-cell-depleted MS patients [3]. The humoral responses after SARS-CoV-2 vaccination or infection in B-cell-depleted MS patients are decreased [4, 5], whereas accumulating evidence suggests that T-cell immunity after vaccination remains largely intact [6, 7]. As lower SARS-CoV-2 antibody titers after vaccination are associated with breakthrough COVID-19 in MS patients [8], the need for reliable and forceful predictors of vaccine responsiveness is obvious.

To date, two markers for predicting humoral responses after SARS-CoV-2 vaccinations in anti-CD20 (mainly ocrelizumab)-treated MS patients have been identified: B-cell count at the moment of vaccination and interval of vaccination versus last infusion [9]. However, as B-cells are fully depleted in the majority of anti-B-cell-treated patients prior to redosing [9], this might be a suboptimal biomarker for timing vaccinations. Also, delaying vaccination until at least 3 months after last infusion may be a suboptimal strategy, as the seroconversion rate can still be low in patients receiving vaccination a relatively long time after last infusion.

In this issue of the *European Journal of Neurology*, Asplund Högelin and colleagues extensively address vaccination responses in B-cell-depleted MS patients [10]. The authors confirm B-cell count as a predictor of seroconversion and they show that B-cell count is a better predictor than interval between last infusion and vaccination in their cohort of 94 MS patients on anti-CD20 therapies of which 82 were using rituximab. The authors also confirm intact T-cell responses after vaccination in the majority of B-cell-depleted patients as reported by others [3, 6, 7]. Apart from B-cell counts and time since last infusion, they introduce rituximab concentrations as a predictor of SARS-CoV-2 seroconversion after vaccination in MS patients treated with rituximab. The authors were the first to show this association between rituximab levels and seroconversion after SARS-CoV-2 vaccination. They present a linear decline in SARS-CoV-2 antibody titers with increased rituximab concentrations, tested 4 weeks after booster vaccination. More than 95% of MS patients below the detection limit of the rituximab enzyme-linked immunosorbent assay (ELISA) assay ($n = 33$) successfully seroconverted. Importantly, anti-CD20 treatment duration varied largely in this cohort (0,4–9.6 years) and about half the patients included in this cohort received treatment >6 months prior to first vaccination.

Obviously, as acknowledged by the authors themselves [10], additional work has to be done to translate their findings to applicability in daily practice. First, clinically relevant drug concentrations and a cut-off drug concentration for seroconversion after vaccination need to be determined and confirmed. Also, the optimal timing of measuring the drug levels in relation to the rituximab infusions needs to be established, taking into account the detection limit of the assay. A pharmacokinetic model, which could predict the decline of drug levels in an individual patient, could further guide the optimal timing for vaccination. Also, similar studies should be performed for other anti-CD20 treatments, that is, ocrelizumab and ofatumumab, the latter possibly being more complicated due to the frequent administration of the drug.

The interesting association between pharmacokinetics and vaccination responses may have clinical relevance for scheduling vaccinations in anti-B-cell-treated patients and might also be important for patients on anti-CD20 drugs other than rituximab. Furthermore, the findings of Asplund Högelin et al. may be extrapolated and could have consequences for patients undergoing vaccinations for other indications than SARS-CoV-2 and with other underlying diseases requiring

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B-cell-depleting agents, (e.g., neuromyelitis optica spectrum disorders and B-cell-depleted hematological and rheumatological patients).

Altogether, drug pharmacokinetics may be a promising addition to timely schedule vaccinations in B-cell-depleted patients. As rituximab concentration could easily be measured in plasma by an ELISA assay, this may be an uncomplicated practical biomarker that helps to increase seroconversion rate, while also avoiding the somewhat unpredictable course of B-cell repopulation at the individual level. Our colleagues from Karolinska have to be congratulated on being the first to identify drug concentration as a potential predictive biomarker for responses after vaccination.

In conclusion, although confirmatory studies are warranted and other anti-B-cell treatments should be involved, rituximab concentration seems to be an easy to use and timely biomarker for the prediction of a humoral response after SARS-CoV-2 vaccination in B-cell-depleted MS patients.

AUTHOR CONTRIBUTIONS

Joep Killestein: Writing – original draft (lead); writing – review and editing (equal). **Zoé van Kempen:** Writing – original draft (supporting); writing – review and editing (equal).

CONFLICT OF INTEREST

Joep Killestein has accepted consulting and speaker fees payed to his institution and research grants from Merck, Biogen, Roche, Teva, Genzyme and Novartis. Zoé van Kempen has nothing to disclose.

DATA AVAILABILITY STATEMENT

Not applicable.

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REFERENCES

1. Sormani MP, De Rossi N, Schiavetti I, et al. Disease modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. *Ann Neurol*. 2021;89(4):780-789. doi:10.1002/ana.26028
2. Simpson-Yap S, De Brouwer E, Kalincik T, et al. Associations of disease-modifying therapies with COVID-19 severity in multiple sclerosis. *Neurology*. 2021;97(19):e1870-e1885. doi:10.1212/WNL.0000000000012753
3. Verstegen NJM, Hagen RR, van den Dijssel J, et al. Immune dynamics in SARS-CoV-2 experienced immunosuppressed rheumatoid arthritis or multiple sclerosis patients vaccinated with mRNA-1273. *Elife*. 2022;11:e77969. doi:10.7554/eLife.77969
4. Achiron A, Mandel M, Dreyer-Alster S, et al. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. *Ther Adv Neurol Disord*. 2021;14:17562864211012835.
5. Louapre C, Ibrahim M, Maillart E, et al. Anti-CD20 therapies decrease humoral immune response to SARS-CoV-2 in patients with multiple sclerosis or neuromyelitis optica spectrum disorders. *J Neurol Neurosurg Psychiatry*. 2022;93(1):24-31. doi:10.1136/jnnp-2021-326904
6. Apostolidis SA, Kakara M, Painter MM, et al. Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. *Nat Med*. 2021;27(11):1990-2001. doi:10.1038/s41591-021-01507-2
7. Palomares Cabeza V, Kummer LYL, Wieske L, et al. Longitudinal T-cell responses after a third SARS-CoV-2 vaccination in patients with multiple sclerosis on ocrelizumab or fingolimod. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(4):e1178. doi:10.1212/NXI.0000000000001178
8. Sormani MP, Schiavetti I, Inglese M, et al. Breakthrough SARS-CoV-2 infections after COVID-19 mRNA vaccination in MS patients on disease modifying therapies during the Delta and the Omicron waves in Italy. *EBioMedicine*. 2022;80:104042. doi:10.1016/j.ebiom.2022.104042
9. van Kempen ZLE, Wieske L, Stalman EW, et al. Longitudinal humoral response after SARS-CoV-2 vaccination in ocrelizumab treated MS patients: to wait and repopulate? *Mult Scler Relat Disord*. 2022;57:103416. doi:10.1016/j.msard.2021.103416
10. Asplund Högelin C, Ruffin N, Pin E, et al. B cell repopulation dynamics and drug pharmacokinetics impact SARS-CoV-2 vaccine efficacy in anti-CD20-treated multiple sclerosis patients. *Eur J Neurol*. 2022;29:3317-3328. doi:10.1111/ene.15492