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Letter

Varicella zoster virus and influenza vaccine antibody titres in patients from MAGNIFY-MS who were treated with cladribine tablets for highly active relapsing multiple sclerosis

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Dear Editor,

The MAGNIFY-MS clinical trial (NCT03364036) aims to determine the onset of action of cladribine tablets 3.5 mg/kg over 2 years (MAVENCLAD®; Merck Europe B.V., Amsterdam, The Netherlands) in patients with highly active relapsing multiple sclerosis. Some patients enrolled in MAGNIFY-MS received vaccinations against varicella zoster virus (VZV) and seasonal influenza as part of their standard of care during the trial, presenting an opportunity to investigate vaccine responses during treatment with cladribine tablets.

Quantitative antibody titre responses to VZV and seasonal influenza vaccines were measured by enzyme-linked immunosorbent and haemagglutination inhibition assays (HAI), respectively. We also explored if the serological response was impacted by lymphocyte counts measured at the time of, or after, vaccination. Ethical approval for MAGNIFY-MS was obtained at each study centre, and all participating patients provided written informed consent.

Blood samples from 14 patients were retrospectively analysed. Three patients received a VZV vaccine (one patient received two doses of the inactivated Shingrix® vaccine; two patients received one dose of the live attenuated Zostavax® vaccine) before initiating treatment with cladribine tablets. All patients mounted seroprotective titres to VZV; the post-vaccination antibody titres of the patient who received Shingrix® were increased $>$ 40-fold over the protective titre at all time points. Seroprotective VZV titres were maintained over the observed post-initiation period with cladribine tablets, despite a marked reduction in lymphocyte counts.

Twelve patients received a seasonal influenza vaccine (one patient received both the VZV and seasonal influenza vaccines). The majority (11/12) had seroprotective antibody titres even before vaccination; post-vaccination seroprotective titres were maintained in those patients. Many patients achieved seroprotection in a short timeframe, that is, between day 21 and 69 from first vaccination. Nine out of 11 patients exhibited a $\geq$ twofold titre increase and 4 out of 11 patients exhibited a $\geq$ fourfold increase for at least one strain of influenza.

We further observed that seroprotection (or an increase in HAI titres) occurred in both patients who were vaccinated early, that is, up to 6 months after a course of cladribine tablets in Years 1 and 2, and late (months 8.5–10.5 of Year 1). Lymphocyte counts in patients vaccinated late after cladribine tablets were within the normal range at that time. In contrast, patients vaccinated early within the first 6 months after a course of cladribine tablets typically showed grade 1 or 2 lymphopenia. Nevertheless, all patients maintained seroprotection.

Our observations are consistent with recent reports of effective COVID-19 immunisation in patients receiving cladribine tablets.[1,2] We hypothesise that unique lymphocyte repopulation kinetics induced by cladribine tablets, including incomplete reduction and subsequent rapid recovery of immature B cells,[3] may explain why vaccination responses appear to resemble those in the normal population while humoral responses in patients treated with other disease-modifying therapies, such as fingolimod and ocrelizumab, with different mechanisms of action, are blunted.[1,2,4,5]

In summary, while results are from a small number of patients vaccinated against VZV and seasonal influenza during treatment with cladribine tablets, they demonstrate consistent humoral responses regardless of timing after treatment administration or total lymphocyte count.

Full results of this analysis can be found in the Supplementary Material.

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Data Availability Statement

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will

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be subject to the Data Sharing Policy of Merck. All requests should be submitted in writing to the data sharing portal of Merck https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licenced, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck will endeavour to gain agreement to share data in response to requests.

Declaration of Conflicting Interests

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HW is member of scientific advisory boards/steering committees for Bayer, Biogen, Merck, Novartis, Roche, Sanofi, and Teva. He has received speaker honoraria and travel support from Bayer, Biogen, CSL Behring, EMD Serono Research and Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA), Fresenius Medical Care, Merck, Omniamed, Novartis, Sanofi, and Teva. He has received compensation as a consultant from Biogen, Merck, Novartis, Omniamed, Roche, and Sanofi. He has received research support from Bayer, Biogen, Merck, Novartis, Sanofi, and Teva, as well as the German Ministry for Education and Research (BMBF), German Research Foundation (DFG), Else Kröner Fresenius Foundation, Fresenius Foundation, Hertie Foundation, Merck, Novartis, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Münster, and RE Children's Foundation.

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Supplemental Material

Supplemental material for this article is available online.

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