Multiple Sclerosis Journal
2022, Vol. 28(13) 2151–2153
DOI: 10.1177/13524585221099413

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

Date received: 27 January 2022; revised: 6 April 2022; accepted: 21 April 2022

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.

Acknowledgements

Medical writing assistance was provided by Joe Ward and Steve Winter of inScience Communications, Springer Healthcare Ltd, UK, and supported by Merck Healthcare KGaA, Darmstadt, Germany.

Data Availability Statement

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

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: **KS** has received research support from Biogen, Merck, and Novartis; speaking honoraria from, and/or served in an advisory role for, Amgen-Gensenta, Biogen, EMD Serono Research and Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA), Merck, Novartis, Roche, Sanofi, and Teva; and remuneration for teaching activities from AcadeMe, Medscape, and the Neurology Academy.

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.

CO-G has received speaker and consultation fees from Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva.

DC is an advisory board member for Almirall, Bayer, Biogen, GW Pharmaceuticals, Merck, Novartis, Roche, Sanofi, and Teva, and received honoraria for speaking or consultation fees from Almirall, Bayer, Biogen, GW Pharmaceuticals, Novartis, Roche, Sanofi, and Teva. He is also the principal investigator in clinical trials for Bayer, Biogen, Merck, Mitsubishi, Novartis, Roche, Sanofi, and Teva. His preclinical and clinical research was supported by grants from Bayer, Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva.

AC is an employee of Cytel Inc., Geneva, Switzerland, which was funded by Merck Healthcare KGaA (Darmstadt, Germany) to perform statistical analyses for this study.

SR and **UB** are employees of Ares Trading S.A., Eysins, Switzerland (an affiliate of Merck KGaA).

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Merck (CrossRef Funder ID: 10.13039/100009945).

ORCID iDs

Klaus Schmierer https://orcid.org/0000-0002-9293-8893

Heinz Wiendl https://orcid.org/0000-0003-4310-3432

Celia Oreja-Guevara https://orcid.org/0000-0002-9221-5716

Supplemental Material

Supplemental material for this article is available online.

References

1. 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.
2. Sormani MP, Inglese M, Schiavetti I, et al. Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. *EBioMedicine* 2021; 72: 103581.
3. Wiendl H, Schmierer K, Hodgkinson S, et al. Characterization of peripheral immune cell dynamics and repopulation patterns in the first 12 months of cladribine tablets treatment: MAGNIFY-MS study. *Neurology* 2021; 96(Suppl. 15): 2235.
4. Kappos L, Mehling M, Arroyo R, et al. Randomized trial of vaccination in fingolimod-treated patients with multiple sclerosis. *Neurology* 2015; 84: 872–879.
5. Baker D, MacDougall A, Kang AS, et al. CD19 B cell repopulation after ocrelizumab, alemtuzumab and cladribine: Implications for SARS-CoV-2 vaccinations in multiple sclerosis. *Mult Scler Relat Disord* 2021; 57: 103448.

Klaus Schmierer[1,2], Heinz Wiendl[3], Celia Oreja-Guevara[4,5], Diego Centonze[6,7], Anita Chudecka[8], Sanjeev Roy[9] and Ursula Boschert[10]

[1]*Centre for Neuroscience, Surgery & Trauma, Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, UK*
[2]*Clinical Board Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, UK*
[3]*Department of Neurology, Institute of Translational Neurology, University of Münster, Münster, Germany*
[4]*Department of Neurology, IdISSC, Hospital Universitario Clinico San Carlos, Madrid, Spain*
[5]*Departamento de Medicina, Universidad Complutense de Madrid, Madrid, Spain*
[6]*Laboratory of Synaptic Immunopathology, Department of Systems Medicine, Tor Vergata University, Rome, Italy*
[7]*Unit of Neurology and Neurorehabilitation, IRCCS Neuromed, Pozzilli, Italy*
[8]*Clinical Research Services, Cytel Inc., Geneva, Switzerland*
[9]*Global Medical Affairs, Ares Trading S.A., Eysins, Switzerland (an affiliate of Merck KGaA)*
[10]*Neurology & Immunology, Ares Trading S.A., Eysins, Switzerland (an affiliate of Merck KGaA)*

Correspondence to:

K Schmierer
Centre for Neuroscience, Surgery & Trauma, Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, 4 Newark Street, London E1 2AT, UK.
k.schmierer@qmul.ac.uk