Letter

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Should anti-CD20 be used as an immune reconstitution therapy?

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In light of the changes in disease-modifying treatment (DMT) practice during the COVID-19 pandemic, the "Controversies in Multiple Sclerosis" section of the April edition of *Multiple Sclerosis Journal* explores whether 6-monthly intervals between anti-CD20 infusions should be maintained or extended. Van Kempen et al.[1] argue in favor and question the efficacy of extended interval dosing as the majority of the studies which have looked at extending infusion intervals are retrospective with short follow-up. On the contrary, Rolfes and Meuth[2] argue that the immunosuppressive effect of anti-CD20 extends beyond the 6-monthly intervals and that extending infusion intervals may offer an opportunity to reduce frequency of infusion and limit consequences of long-term immune suppression. However, both parties do not discuss a very valid third option, namely to use anti-CD20 as an immune reconstitution therapy (IRT). This would imply that anti-CD20 is administered for a limited number of infusion cycles followed by a treatment-free period during which disease recurrence is monitored by clinical and radiological biomarkers. We argue that exploitation of anti-CD20 treatment as an IRT could result in important benefits for people with multiple sclerosis (pwMS) treated with this therapy.

First, there is evidence that using anti-CD20 as an IRT could provide a better balance between risks and benefits. In an analysis of the ocrelizumab (OCR) phase-2 extension trial, it became clear that the annualized relapse rate (ARR) remained low during the drug-free 18-month follow-up period after 3 or 4 treatment cycles in 101 individuals.[3] Moreover, the ARR was comparable to the ARR reported in the 5-year follow-up open-label extension study of pwMS on 6-monthly infusions.[4] During the treatment-free anti-CD20 period, no new T1-gadolinium-enhancing or T2-lesions were detected, and there were less adverse events and infection as during the treated period.[3] In 26 pwMS, the phase-1 (RTX) rituximab extension study also reported a maintained anti-inflammatory benefit 12 months after the last infusion.[5] Of note, two other multiple sclerosis (MS) DMTs are currently used as an IRT in routine clinical practice (i.e. alemtuzumab and cladribine). Pivotal trials of cladribine and alemtuzumab showed long-lasting clinical efficacy in controlling relapses after two cycles of treatment with a 1-year interval[6–8] which was similar to OCR in a network meta-analysis of the phase III trials.[9] Importantly, the therapeutic effect of cladribine and alemtuzumab is deemed to be related to their shared and profound effect on B cell counts as previous $CD4^+$ depletion studies have been ineffective in controlling MS disease activity.[10,11] Along this line, the persistent and long-term depletion of memory B cells has been put forward as a key mechanism of action driving long-term efficacy of IRTs.[12,13]

Second, chronic B-cell depletion renders pwMS more susceptible for common and severe infections compared to other DMTs. In a pre-COVID-19 nationwide Swedish cohort, RTX-treated pwMS exhibited the highest rate of serious infections compared to other DMTs (hazard ratio (HR), 1.70; 95% confidence interval (CI), 1.11–2.61).[14] This is especially relevant for the most vulnerable individuals who have urinary tract dysfunction or swallowing difficulties.[15,16] Observational cohorts during the COVID-19 pandemic have shown a more than twofold higher incidence of severe infections and intensive care unit (ICU) admissions in OCR compared to other DMTs.[17,18] One of the anti-CD20 specific risk factors for severe infections might be the occurrence of IgG deficiency which was present in 7.1% of pwMS after 6 years of treatment.[19] In addition, anti-CD20 treatment interferes with adequate IgG antibody response to vaccines.[20,21] This observation has been highlighted during the COVID-19 pandemic. Several investigators showed that anti-CD20 therapy significantly reduced in most pwMS anti-SARS-CoV-2 spike and receptor-binding domain-specific antibodies and memory B-cell responses.[22,23] No data exist on vaccine efficacy when consistently extending anti-CD20 infusion intervals, but in several studies, there is a correlation with time to last OCR infusion.[22,24] In contrast, most pwMS treated with anti-CD20 mAb generated antigen-specific $CD4^+$ and $CD8^+$ T-cell responses following vaccination.[22,23] These observations indicate that chronic anti-CD20 allows virus elimination but disturbs the immunological memory and thus prevention of repeat infection in people infected in the past or after vaccination.

In summary, there is no observational or mechanistic evidence that continued infusions would be necessary

to control MS inflammation. Therefore, we argue that the use of anti-CD20 treatment as an IRT should be investigated. We acknowledge that there is no real-time biomarker available for MS disease recurrence, but this is equally true for pwMS treated with cladribine and alemtuzumab. Although confirmation is needed in standardized trials, post hoc analyses of the phase-3 OCR data have suggested that lower body mass index (BMI) and thus a higher exposure to anti-CD20 could be associated with slower disability progression.[25] This observation is perfectly compatible with an IRT strategy in which anti-CD20 infusions are BMI-adjusted for three or four cycles.

Declaration of Conflicting Interests

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ORCID iDs

Ide Smets https://orcid.org/0000-0001-8174-2898
Beatrijs HA Wokke https://orcid.org/0000-0002-2616-8464
Joost Smolders https://orcid.org/0000-0001-9766-8661

References

1. Van Kempen ZLE, Hogenboom L and Killestein J. Stable multiple sclerosis patients on anti-CD20 therapy should go on extended interval dosing: NO. *Mult Scler* 2022; 28: 693–695.
2. Rolfes L and Meuth SG. Stable multiple sclerosis patients on anti-CD20 therapy should go on extended interval dosing: "Yes." *Mult Scler* 2022; 28(5): 691–693.
3. Baker D, Pryce G, James LK, et al. The ocrelizumab phase II extension trial suggests the potential to improve the risk: Benefit balance in multiple sclerosis. *Mult Scler Relat Disord* 2020; 44: 102279.
4. Hauser SL, Kappos L, Arnold DL, et al. Five years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension. *Neurology* 2020; 95: e1854–e1867.
5. Bar-Or A, Calabresi PA, Arnold D, et al. Rituximab in relapsing-remitting multiple sclerosis: A 72-week, open-label, phase I trial. *Ann Neurol* 2008; 63(3): 395–400.
6. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: A randomised controlled phase 3 trial. *Lancet* 2012; 380: 1829–1839.
7. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: A randomised controlled phase 3 trial. *Lancet* 2012; 380: 1819–1828.
8. Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 416–426.
9. Samjoo IA, Worthington E, Drudge C, et al. Efficacy classification of modern therapies in multiple sclerosis. *J Comp Eff Res* 2021; 10(6): 495–507.
10. Baker D, Herrod SS, Alvarez-Gonzalez C, et al. Both cladribine and alemtuzumab may effect MS via B-cell depletion. *Neurol Neuroimmunol Neuroinflamm* 2017; 4(4): e360.
11. van Oosten BW, Lai M, Hodgkinson S, et al. Treatment of multiple sclerosis with the monoclonal anti-CD4 antibody cM-T412: Results of a randomized, double-blind, placebo-controlled, MR-monitored phase II trial. *Neurology* 1997; 49(2): 351–357.
12. Baker D, Herrod SS, Alvarez-Gonzalez C, et al. Interpreting lymphocyte reconstitution data from the pivotal phase 3 trials of alemtuzumab. *JAMA Neurol* 2017; 74: 961–969.
13. Sellner J and Rommer PS. Immunological consequences of "immune reconstitution therapy" in multiple sclerosis: A systematic review. *Autoimmun Rev* 2020; 19(4): 102492.
14. Luna G, Alping P, Burman J, et al. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. *JAMA Neurol* 2020; 77: 184–191.
15. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 2017; 376: 209–220.
16. Avouac A, Maarouf A, Stellmann JP, et al. Rituximab-induced hypogammaglobulinemia and infections in AQP4 and MOG antibody-associated diseases. *Neurol Neuroimmunol Neuroinflamm* 2021; 8(3): e977.
17. 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.

18. 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: e1870–e1885.

19. Derfuss T, Weber M, Hughes R, et al. P36 serum immunoglobulin levels and risk of serious infections in the pivotal phase III trials of ocrelizumab in multiple sclerosis and their open-label extensions. *Clin Neurophysiol* 2020; 131: e196.

20. Bingham CO, 3rd, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: Results from a controlled clinical trial. *Arthritis Rheum* 2010; 62(1): 64–74.

21. Bar-Or A, Calkwood JC, Chognot C, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: The VELOCE Study. *Neurology* 2020; 95: e1999–e2008.

22. 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.

23. Brill L, Rechtman A, Zveik O, et al. Humoral and T-cell response to SARS-CoV-2 vaccination in patients with multiple sclerosis treated with ocrelizumab. *JAMA Neurol* 2021; 78: 1510–1514.

24. Tallantyre EC, Vickaryous N, Anderson V, et al. COVID-19 vaccine response in people with multiple sclerosis. *Ann Neurol* 2022; 91: 89–100.

25. Kletzl H, Gibiansky E, Petry C, et al. Pharmacokinetics, pharmacodynamics and exposure-response analyses of ocrelizumab in patients with multiple sclerosis (N4.001). *Neurology* 2019; 92: N4001.

***Ide Smets*[1], *Beatrijs Wokke*[1] *and Joost Smolders*[1]**

[1]MS Center ErasMS, Departments of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence to:

I Smets
MS Center ErasMS, Departments of Neurology, Erasmus Medical Center, Doctor Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.
i.smets@erasmusmc.nl