5. Bsteh G, Feige J, Ehling R, et al. Discontinuation of disease-modifying therapies in multiple sclerosis – Clinical outcome and prognostic factors. *Mult Scler* 2017; 23(9): 1241–1248.
6. Rolfes L and Meuth SG. Stable multiple sclerosis patients on anti-CD20 therapy should go on extended interval dosing— 'Yes'. *Mult Scler J*. Epub ahead of print 21 December 2021. DOI: 10.1177/13524585211055593.
7. Kempen ZLE, van Toorop AA, Sellebjerg F, et al. Extended dosing of monoclonal antibodies in multiple sclerosis. *Mult Scler J*. Epub ahead of print 24 December 2021. DOI: 10.1177/13524585211065711.
8. Tallantyre EC, Vickaryous N, Anderson V, et al. COVID-19 vaccine response in people with multiple sclerosis. *Ann Neurol* 2022; 91(1): 89–100.
9. Jolles S, Chapel H and Litzman J. When to initiate immunoglobulin replacement therapy (IGRT) in antibody deficiency: A practical approach. *Clin Exp Immunol* 2017; 188(3): 333–341.
10. Seery N, Sharmin S, Li V, et al. Predicting infection risk in multiple sclerosis patients treated with ocrelizumab: A retrospective cohort study. *CNS Drugs* 2021; 35(8): 907–918.

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Long-term treatment with anti-CD20 monoclonal antibodies is untenable because of risk: Commentary

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The crucial role of B-cells in the immunopathogenesis of multiple sclerosis (MS) was revealed in the first trials of monoclonal antibodies (mAbs) targeting CD20 on B-cells.[1,2] Since then, accumulating evidence confirms that the three major anti-CD20 therapies, rituximab, ocrelizumab, and ofatumumab, are all highly effective, reducing relapse rate and lesion formation on magnetic resonance imaging (MRI). Due to the low passage of mAbs over the blood–brain barrier, the mechanism of action from anti-CD20 therapies is mainly in the periphery, giving rise to undetectable levels of B-cells in blood. Nevertheless, in addition to a strong anti-inflammatory effect, an effect on degeneration is also obtained, halting disability worsening and the rate of brain and spinal cord atrophy. This effect is probably secondary to immunosuppression, and trials of rituximab and ocrelizumab in primary progressive MS suggest that lower progression rate is mainly achieved in patients with signs of inflammatory activity. However, safety of anti-CD20 therapies has been a concern in pivotal trials, their open label extensions, as well as in observational studies, in particular the risk of serious infections.[3] This risk has also received attention during the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic where several reports unanimously confirm an increased risk for severe COVID-19 (coronavirus disease 2019) infection[4] and a lower IgG antibody response after vaccination in rituximab- and ocrelizumab-treated patients.[5] This raises important critical questions on the selection of patients, monitoring safety and possible strategies to reduce risks of serious infection and improve humoral vaccine response during anti-CD20 treatment.

Dr Zecca and Dr Gobbi argue that long-term anti-CD20 mAb therapies are untenable because of the progressively increased risk of adverse event burden, including serious and opportunistic infections, malignancies, and impaired immune response to vaccines.[6] To mitigate the risk of serious adverse events, they suggest anti-CD20 as an induction therapy or modified anti-CD20 dosing schedules. In contrast, Dr Tallantyre considers that the benefits of long-term anti-CD20 outweigh the risks.[7] The risk of secondary IgG deficiency is limited, and although the antibody response to vaccination is impaired during anti-CD20 therapy, the T-cell response is maintained,[8] which should reduce the risk for severe infection. In patients with hypogammaglobulinemia, Tallantyre suggests the use of serology surveillance, prophylactic antibiotics, or immunoglobulin substitution.

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There seem to be two major strategies to mitigate the risk with anti-CD20 therapies in MS. First, a selection of patients, suggested by both the Yes and No positions, should improve safety. Thus, older age and age-related factors including severe disability, immunosenescence, comorbidities, and use of other immunosuppressive therapies should limit the use of anti-CD20 treatment. The second strategy is the adaptation of the anti-CD20 dosing schedule. High efficacy of rituximab treatment in MS seems to be maintained with a comparable low dose[9] and extended dosing interval or even discontinuation did not increase the risk of reappearance of disease activity in a retrospective study.[10] Thus, improved safety of anti-CD20 treatment should be achievable. A major advantage with anti-CD20 therapies is the possibility to monitor B-cell counts and IgG levels in blood and thereby allowing modifications of dosing schedules to reduce risks and improve humoral response after vaccination.

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References

1. 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.
2. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008; 358: 676–688.
3. 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.
4. Schiavetti I, Ponzano M, Signori A, et al. Severe outcomes of COVID-19 among patients with multiple sclerosis under anti-CD-20 therapies: A systematic review and meta-analysis. *Mult Scler Relat Disord* 2022; 57: 103358.
5. 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.
6. Zecca C and Gobbi C. Long-term treatment with anti-CD20 monoclonal antibodies is untenable because of risk—YES. *Mult Scler J*. Epub ahead of print 29 April 2022. DOI: 10.1177/13524585221091404.
7. Tallantyre E. Long-term treatment with anti-CD20 monoclonal antibodies is untenable because of risk—No. *Mult Scler J*. Epub ahead of print 29 April 2022. DOI: 10.1177/13524585221091404.
8. Asplund Hogelin K, Ruffin N, Pin E, et al. Development of humoral and cellular immunological memory against SARS-CoV-2 despite B cell depleting treatment in multiple sclerosis. *iScience* 2021; 24: 103078.
9. Granqvist M, Boremalm M, Poorghobad A, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. *JAMA Neurol* 2018; 75: 320–327.
10. Boremalm M, Sundström P and Salzer J. Discontinuation and dose reduction of rituximab in relapsing-remitting multiple sclerosis. *J Neurol* 2021; 268(6): 2161–2168.