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Title: Long-term treatment with anti-CD20 monoclonal antibodies is untenable because of risk – No

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Since the emergence of disease modifying therapies (DMTs) for multiple sclerosis (MS) in the 1980s, the therapeutic landscape has evolved considerably. People diagnosed with relapsing MS (RMS) now have access to a range of therapies, and people with progressive MS have one or more DMT options, which have been shown to improve clinical outcomes. While the therapeutic landscape for RMS is now somewhat crowded, this affords individuals choice according to their preferences regarding mode of administration, efficacy, side-effect and safety profile, and family plans.

When ocrelizumab became the first anti-CD20 to receive a US/ European licence for MS in 2017/2018, it appeared to offer convenience, high efficacy, and a favourable safety profile according to Phase 3 trial data. Off-licence use of rituximab for MS and neuromyelitis optica (NMO) was already happening in several countries, based on similarly favourable observational data. However, emerging data from real-world observational studies and open-label extension trials have started to raise questions about the safety of indefinite use of anti-CD20s for MS.(1) Secondary antibody deficiency is now a well-recognised treatment-related risk of anti-CD20s, which appears to be linked to risk of clinically relevant infections. However, during open-label extension studies of licensed anti-CD20s, the rates of people experiencing low IgG are relatively low (ofatumumab 1.5% at 3.5 years; ocrelizumab 5.4% at 5 years). Rates of people with MS experiencing IgM below the lower limit of normal are higher (ofatumumab 23.1% at 3.5 years; ocrelizumab 29.5% at 5 years), but the clinical significance of low IgM with regards to infection remains uncertain. Safety data on ofatumumab and other emerging anti-CD20s are inevitably limited by fewer patient-years of experience. This is particularly relevant to the cumulative nature of some anti-CD20 related risks. These caveats mean that early signals that the safety profile of ofatumumab may be more favourable, making it suitable for longer-term use, should be interpreted with caution.(2)

Attenuated humoral response to vaccination is now well-recognised in people receiving anti-CD20 DMTs, particularly following intense study of vaccine response during the COVID-19 pandemic. However, T-cell responses to vaccination appear to be maintained in the majority of those on anti-CD20 medications, and seroconversion can be achieved with additional booster vaccination in a proportion, suggesting that the attenuated humoral responses can be compensated to some extent.(3)

The question of the feasibility of long-term anti-CD20 treatment for MS can be viewed in several ways. The optimum duration of any MS DMT remains an area of controversy. Natural history data demonstrate an expected decline in annualised relapse rate over time,(4) so that de-escalation in the context of suppressed disease activity seems an appropriate feature of any MS treatment algorithm. However, stopping criteria are not yet universally agreed, and some individuals demonstrate an ongoing need for long-term DMT, based on return of inflammatory disease activity when DMT is stopped or de-escalated after a period of stability.(5)

In people with MS where anti-CD20 therapy remains the preferred approach, risk-mitigation strategies are likely to be capable of enabling long-term use. The use of adaptive dosing of anti-CD20s (monitoring the return of B-cells to guide dosing interval), or simply extending the interval between anti-CD20 doses, is gaining increasing support.(6) This approach

parallels efforts to use extended interval dosing to mitigate risk of PML in people using natalizumab for MS, potentially enabling longer-term use. Several observational studies have now demonstrated that adaptive dosing of rituximab and ocrelizumab for neuroinflammatory disease appear to maintain efficacy against new inflammatory disease activity, while improving safety outcomes.(7) We and others have shown that longer interval since last anti-CD20 infusion has also been shown to associate with more favourable humoral vaccine response.(8) On the other hand, post hoc analysis of the Phase 2 ocrelizumab trial has prompted randomised trials of standard versus higher dose ocrelizumab, based on the suggestion that higher doses may improve efficacy measured by disability progression, casting doubt on the rationale for adaptive dosing. Furthermore, it remains unclear how adaptive dosing would work in practice for ofatumumab, which is administered once a month.

Risk mitigation where secondary antibody deficiency has already arisen, but anti-CD20 therapy is nevertheless felt to offer ongoing benefits, could be achieved in other ways. Routine surveillance for infection, used routinely in cases of Primary Antibody Deficiency, should be extended to those with secondary antibody deficiency.(9) Using this approach, serum immunoglobulin levels, disease-specific antibody titres (e.g. directed at *haemophilus influenzae* or pneumococcus), vaccine response and infection burden can all be used to inform appropriate use of rescue or prophylactic antibiotics, or even Immunoglobulin Replacement Therapy. Pausing or rescheduling anti-CD20 treatment to allow more efficacious vaccination is an area worthy of further investigation, which may also improve the safety profile of anti-CD20s, allowing longer use.

Finally, the safety signals detected at group level in people receiving anti-CD20 therapies do not seem to apply to all individuals; the minority appear to experience untenable risks during long-term extension studies. Infection risk on anti-CD20 therapy has also been shown to vary according to factors including serum IgG, older age, longer disease duration and higher disability.(10) Further work exploring the individual risk factors for secondary antibody deficiency and infection on anti-CD20 may allow us to identify individuals who are more suitable for long-term treatment.

Treatment-related risks must be balanced against anticipated benefits, on an individual basis. To judge that those risks have become untenable would require all the benefits of treatment to be offset. Aside from the convenience, compliance and tolerability benefits of anti-CD20 DMTs, these products address contemporary pathological evidence that B-cells are key drivers of neuronal loss, and that opportunities for improvement in long-term disability outcomes may be missed if we only target short-term control of focal inflammation.

Declaration of Conflicting Interests

The author declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Tallantyre has consulted for Biogen, Janssen Pharmaceuticals, Merck, Novartis, and Roche.

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