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Alemtuzumab; balancing risks

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Alemtuzumab was the first humanised monoclonal antibody developed in 1979 and initially used in the treatment of lymphoid malignancies. However, its mode of action (peripheral complement mediated CD52 lysis and immune reconstitution) offered opportunities across a range of autoimmune diseases including MS. Initial open label use reported promising results for relapsing MS, but with early recognition of adverse events, particularly autoimmune thyroid disease¹. It also offered some unique and interesting mechanistic insights into the biology of MS. Specifically the role of T-cells and a proposal for a window of therapeutic opportunity during which early and highly effective treatment could offer some long-term advantages². A hypothesis that has been followed by supportive real-world evidence and is now the focus of two large international trials due to report soon. Large phase 3 trials were reported in 2012 demonstrating impressive efficacy^{3,4} and the drug was subsequently approved by regulatory authorities and widely used between 2014 and 2020. Although the indications for treatment and views on the point at which it should be used along the therapeutic pathway varied considerably.

The high rate of adverse events was well-recognised and had been documented in the clinical trials and appropriate safety monitoring and patient education programs were developed. Most of the adverse events related to thyroid disease, but there was also a low incidence of more significant disorders including idiopathic thrombocytopenic purpura, Goodpasture's syndrome, atypical infections and diffuse alveolar haemorrhage (DAH) that required prompt intervention. In a field that was traditionally risk adverse, there was some understandable nervousness about

its use, but the risk of adverse events was balanced against high efficacy and limited treatment choices.

In 2018 following reports of serious peri-infusion cardiovascular side effects, it was felt that the risk/benefit balance had changed. The FDA issued new advice and a change of indication to restrict its use to those patients with rapidly evolving or highly active MS. Together with the development of a range of alternative highly effective DMTs over recent years the overall effect has been that Alemtuzumab is now used sparingly and generally only in highly specialised centres.

However, in the FDA guidance one of the stated contraindications to treatment is the presence of an alternative autoimmune disorder. The reasons for this decision are unclear and whether it also relates to patients who have already received a first cycle of Alemtuzumab. For instance, it could be argued that patients with preexisting thyroid disease are at less risk of adverse events and evidence suggests that risks of treatment with alemtuzumab are ‘front-loaded’ and reduce over time⁵. In this month’s journal, Zhao et al report on a patient with MS who developed DAH during a first cycle of alemtuzumab, but on whom the decision was made to offer the second cycle to one year later which was completed uneventfully. The aetiology of DAH, together with other autoimmune adverse effects of alemtuzumab remains poorly understood, but with appropriate vigilance and monitoring most can be treated and should not necessarily be a contraindication to completing treatment cycles.

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