Can immune reprogramming with alemtuzumab induce permanent remission in multiple sclerosis?

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Disease-modifying therapies (DMTs) for multiple sclerosis (MS) have developed tremendously over the last 2 decades. Currently, more than 16 different products targeting various immunologic components have been approved for MS treatment in several countries.

The high number of MS treatments has made the management of patients increasingly complex. Two main therapeutic strategies are currently adopted in the clinical setting: (1) escalation (or optimization) therapy or (2) induction (or immune reset) therapy (figure). In the escalation/optimization strategy, alemtuzumab is recommended as a second- or third-line therapy to patients who have had an inadequate response to initial DMTs. In the induction strategy, it has instead been argued by some investigators that alemtuzumab should be used as a first-line agent with the intention of inducing long-term disease stability. However, long-term follow-up studies are needed to know what percentage of patients have a durable response to alemtuzumab without the development of severe side effects.

Alemtuzumab is an immune-depleting therapy that has 3 major parts to its mechanism of action: (1) selective targeting of CD52 on T and B cells, and to a lesser extent, innate immune cells; (2) immediate depletion of immune cells; and (3) perhaps the most important and least understood part, a phase of immune cell repopulation. Depletion of CD52+ immune cells occurs mainly in the periphery and subsequent effects are translated to the CNS.[1] Investigation of the long-term effects of alemtuzumab on various subtypes of immune cells, such as T effector memory and resident memory T cells, illustrates aspects of repopulation and immune reprogramming.[2] The drug administration route and dosing, the persistently low CD4 and CD8 T-helper cell levels, and the occurrence of secondary autoimmunity during the phase of immune cell repopulation suggest that alemtuzumab induces a reprogrammed immune repertoire. Alemtuzumab thus might produce a durable therapeutic response as a consequence of a permanent rebalancing of the immune system.

In this issue of *Neurology*®, Havrdova et al.[3] and Coles et al.[4] report efficacy and safety results of 3-year extension studies of both Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis I and II (CARE-MS I and II) trials. These were 2-year, phase III, randomized, active-controlled trials that compared alemtuzumab with interferon-β-1a in patients with relapsing-remitting MS and active disease (defined as ≥2 relapses in the last 2 years and ≥1 relapse in the last year). The main difference between the 2 trials is that CARE-MS I patients had never received disease-modifying treatment, while CARE-MS II patients had relapsed after prior treatment with other therapies. In both, treatment with alemtuzumab consisted of 5 daily 12 mg infusions at the start of therapy, and another round occurring 1 year later consisting of 3 daily 12 mg infusions. Analysis of the extension studies showed that the annualized relapse rate at 5 years was 0.15 in CARE-MS I and 0.18 in CARE-MS II. The cumulative fraction of participants with no evidence of clinical and MRI disease activity over years 3–5, referred to as no evidence of disease activity (NEDA), was 39.5% in CARE-MS I and 27% in CARE-MS II. Importantly, 67.3% and 55.5% of participants enrolled into the extension studies did not require any DMT over 3 years after the second alemtuzumab treatment, and it can be argued that they were experiencing a drug-treatment-free remission (figure); the remaining 32.7% and 44.5% of patients received treatment with alemtuzumab or another DMT. A total of 33% and 42.9% of patients showed a confirmed disability improvement (defined as ≥1-point Expanded Disability Status Scale decrease from a baseline score ≥2.0) over 5 years. The median yearly brain parenchymal fraction change was −0.2 in the extension of CARE-MS I and −0.07 in the extension of CARE-MS II.

These efficacy results must be considered with some caution, however, considering that there are biases typical of extension studies with open-label designs, including the lack of blinding and the lack of

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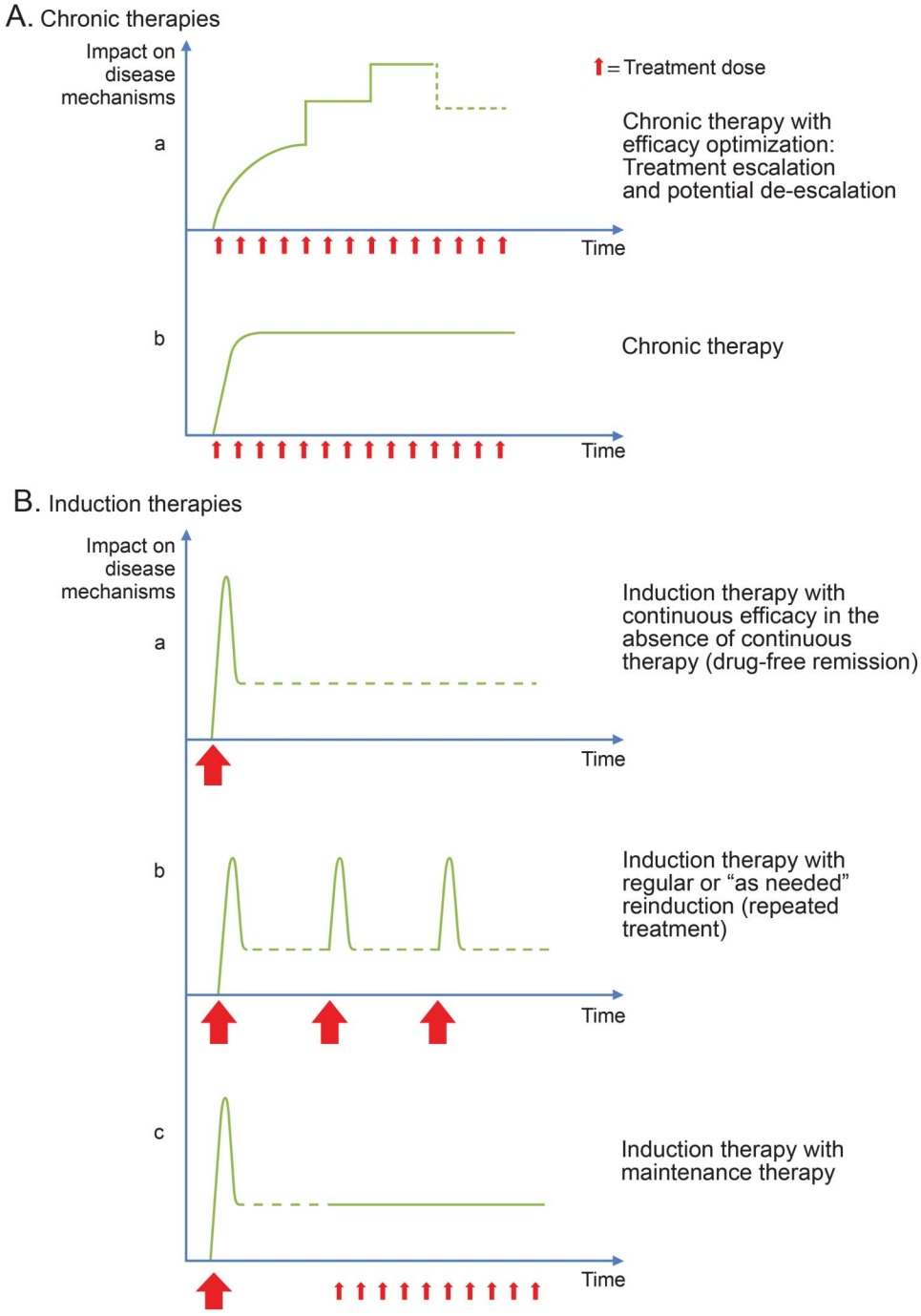
Figure Overview of therapeutic concepts in multiple sclerosis: Chronic vs induction therapies



(A) Chronic therapy strategies requiring the continuous application of treatments over time, with a possibility for optimization/escalation of treatment. (B) Induction therapies are applied with less frequent and more disease pathogenesis intervening doses that are followed by a no continuation therapy (a), repeated induction treatments on a regular or as-needed basis (b), or maintenance therapy with maintenance treatment (c).

a control group. In addition, 4.9% of CARE-MS I patients and 7.1% of CARE-MS II patients declined to be enrolled in the extension studies; while this is an unusually high enrollment rate for an extension study, these percentages should be kept in mind and perhaps subtracted from the reported rates of NEDA and percentage of patients who did not require treatment with a DMT over the 3 years after alemtuzumab treatment. Since the decision to continue treatment with alemtuzumab or any other drug was left to the treating physicians and patients, patients may have remained untreated despite disease progression (which was permissible in the extension study), and the opinions of nonblinded investigators could have influenced the detection of disease activity.

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Extension studies are undoubtedly useful in improving our knowledge of side effects of new medications. This is especially relevant for alemtuzumab, whose key adverse events include infusion reactions, immune-mediated thyroid disease, immune thrombocytopenia (ITP), and glomerulonephritis. Alemtuzumab may also be associated with other serious complications, as suggested by recent cases of *Listeriosis monocytogenes*, cytomegalovirus syndrome, pulmonary and CNS nocardiosis, and B-cell-mediated CNS disease.[5–7] Both extension studies reported new findings in respect to the core studies, which included a substantial risk of herpes zoster reactivation, with 25 new cases in the extension of CARE-MS I and 35 cases in the extension of CARE-MS II, and a relatively high 5-year incidence of thyroid autoimmunity (40.7% and 37.7%, respectively). Particular attention should be given to papillary thyroid carcinoma, with 1 new case in the extension of CARE-MS I and 2 new cases in the extension of CARE-MS II. Eleven new cases of ITP occurred overall in the extension studies and 1 case of nephropathy was seen at year 3 in the extension of the CARE-MS I trial. Whether additional serious adverse events will develop beyond 3 years after the last infusion of alemtuzumab remains to be determined.

Overall, the extension studies of CARE-MS I and CARE-MS II trials suggest that therapy-free remission can be achieved in over 50% of patients following 2 courses of alemtuzumab, indicating that a sustained immunologic reprogramming of the disturbed immune repertoire can be achieved in many patients. Further follow-up is needed to determine how long this immunologic reprogramming will last. Several challenges remain in the use of alemtuzumab. These include the need to identify prognostic biomarkers that identify patients who are more likely to benefit from an induction treatment strategy and the need for longer observation periods to confirm the safety profile of alemtuzumab, which is crucial in selecting this drug over another highly efficacious therapy, natalizumab.[8] An interesting question that, if addressed, may shed some light into the pathogenesis of MS is why some patients show disease worsening despite immune-depleting therapy.

The possibility of inducing a long-term or even permanent drug-free remission in people with relapsing-remitting MS with alemtuzumab is exciting and novel in MS therapy. The challenge is to define which patients warrant treatment with this potent therapy and identifying ways to mitigate serious side effects.

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