EDITORIAL

Defining response profiles after alemtuzumab

Rare paradoxical disease exacerbation

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Activation of disease during therapy with alemtuzumab in 3 patients with multiple sclerosis

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Alemtuzumab is a humanized monoclonal antibody that causes a rapid but long-lasting depletion of the CD52-bearing lymphoid lineage. Selective pulsed depletion is followed by a complex pattern of immune cell reconstitution that reflects the reshaping and potential reprogramming of immune networks, including the development of tolerance.[1] Recent studies showed that pulsed-immune reconstitution therapy with alemtuzumab can produce durable efficacy after 2 courses of treatment (year 1 and 2).[2–5]

In this issue of *Neurology*®, Wehrum et al.[6] present 3 retrospective cases of patients treated with alemtuzumab who experienced activation of the disease following treatment initiation, adding to previous case reports.[7–9] Paradoxical disease activation occurred in patients with highly active relapsing-remitting multiple sclerosis (MS) with long disease history (7–15 years; Expanded Disability Status Scale 1.0–2.0) around 6 months after treatment initiation, when B cells may have repopulated to levels higher than baseline, although T cells remain heavily depleted. All 3 cases represent highly active patients who had failed on several previous therapies. In each case, B-cell-targeted therapies (plasmapheresis or rituximab, or both) led to sustained disease control.

What characterizes, defines, and predicts response after alemtuzumab (figure)? The best scenario is a complete and durable response (type I), ideally with no evidence of disease activity (NEDA) and requiring no additional treatment. This outcome is frequent and occurs in clinical studies in approximately 50% of patients. Type II comprises a complete initial response with return of some disease activity after the second treatment cycle; retreatment is given on an as-needed basis.[2,4] This indicates that repopulation is not always associated with a permanent rebalance of immune tolerance (due to strong antigenic drive, strong genetic predisposition factors, or the influence of unknown environmental and lifestyle factors within the reconstitution phase). Type III represents a partial response where patients do not respond after the first infusion (as a consequence of disease activity, severity, pretreatment, or time from last treatment), but acquire a complete (durable or transient) response later on (in year 2). Alternatively, the patient shows a partial response (e.g., reflected by incomplete NEDA measures) that persists in year 2. Presence of disease activity after therapy in year 1 is not uncommon in clinical practice, as was observed in clinical trials (~15% in the Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis, Study I [CARE-MS I] study with treatment-naive patients). The mode of action of alemtuzumab allows us to speculate that reconstitution of the immune regulatory network architecture is time-dependent and may be complete or nearly so after 2 treatment cycles. Type IV represents paradoxical disease exacerbation after one course occurring within the first 6–12 months of treatment. This is rare, but has been described in these and other case reports (figure).[7,8]

These findings urge us to understand the pathophysiology underlying these responder profiles, so as to deduce predictive or therapeutic markers. Some patients had increased B-cell counts and gadolinium ring-enhancing cerebral lesions; the authors speculated that an overshooting of the B-cell recovery response might be associated with disease aggravation. B cells repopulate

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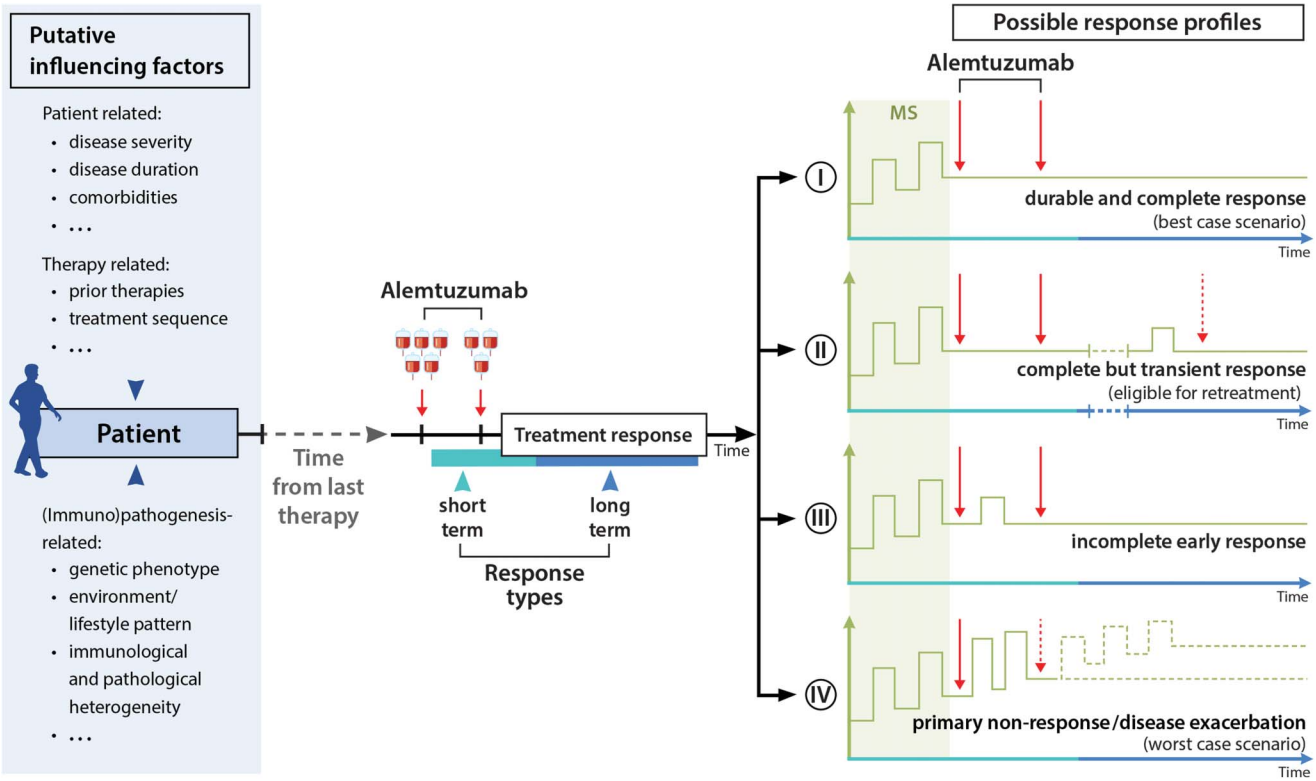
Figure Alemtuzumab response



MS = multiple sclerosis.

faster than T cells in alemtuzumab-treated patients, and B-cell overdrive could trigger disease exacerbation or secondary autoimmunity.[10] However, in the CARE-MS trial data, the absolute and relative lymphocyte counts were not associated with distinct response profiles or the likelihood to develop secondary autoimmune events. Also, the vast majority of patients do not show disease exacerbation despite a similar pattern of quantitative B-cell repopulation. Notably, some patients were successfully treated with a B-cell-depleting therapy (rituximab). Perhaps further study of B-cell subsets that have unique cytokine or memory profiles will shed more light on the potential role of B cells in disease activation.

Interestingly, some patients with neuromyelitis optica spectrum disorder (NMOSD) showed increased disease activity following alemtuzumab.[11] In one fatal instance, disease exacerbation was accompanied by a massive monocyte infiltration into the CNS.[12] These findings might be interpreted as an activation of the innate immune system (e.g., monocytes) due to an absence of suppression by the adaptive immune system. In one case, rituximab and mycophenolate mofetil stabilized a patient from further relapses and disease progression, suggesting that alemtuzumab should be used with caution in patients with NMOSD.

Response to alemtuzumab has to be interpreted in the context of prior treatments and their mode of action. Treatment with leukocyte sequestrating agents (natalizumab and fingolimod) prior to immune depletion represents a challenge, since cessation of therapy carries risks for disease reactivation/exacerbation, carrying over of treatment-related risks (especially progressive multifocal leukoencephalopathy), and the onset of action of subsequent immune reconstituting treatments. Of note, the majority of patients showing disease exacerbation under alemtuzumab treatment were switched from fingolimod or had received fingolimod in the past, leading to the hypothesis that a substantial number of lymphocyte subsets still remained separated in the lymph nodes. Alemtuzumab depletes CD52-expressing immune cells particularly in the intravascular compartment, but much less in lymph nodes. Thus, when leukocytes are released when alemtuzumab is no longer present, these egressed cells might initiate rebound inflammatory activity, as with fingolimod discontinuation.[9] Although B cells and their repopulation patterns are attractive candidates to explain the immunology underlying primary disease exacerbation after alemtuzumab, this view might be too simplistic. Alemtuzumab alters many immune cell populations quantitatively but also qualitatively, including adaptive and innate immune regulatory networks.[13] Understanding changes in the immunome and its reeducation on a higher systems level will probably be needed to elucidate MS-related immunologic heterogeneity, characteristics of treatment responses, or the propensity for adverse events following pulsed immune reconstitution therapy.

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Taken together, a patient's response profile following alemtuzumab seems to be affected by 1) severity and activity of the individual disease course, duration of disease, prior therapies, and their specific mode of action; 2) the gap among past, current, and subsequent therapies; and 3) the immunopathologic heterogeneity of MS. Again, biomarkers indicating prognosis, therapeutic response, and risk factors for optimal and durable response vs early treatment failures are highly warranted and will pave the way to understand disease heterogeneity in MS.

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