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Maximally tolerated versus minimally effective dose: the case of rituximab in multiple sclerosis

Sir,

A phase II randomized controlled trial of high-dose rituximab—a chimeric antibody directed against the CD20 antigen present on B cells—demonstrated remarkable efficacy in relapsing-remitting multiple sclerosis (MS), both in terms of gadolinium-enhanced lesions and frequency of clinical relapse.[1] Although currently US Food and Drug Administration (FDA) approved for use in non-Hodgkin's lymphoma (NHL) and rheumatoid arthritis, rituximab is commonly used as off-label treatment for severe MS. Dosing regimens have been adopted from NHL treatment protocols based on the maximum tolerated dose—375 mg/m^2 given weekly for 4 weeks or a fixed dose of 1 g administered twice, 2 weeks apart. High-dose therapy often results in B-cell depletion for approximately 12 months,[2] and has been associated with the development of progressive multifocal leukoencephalopathy in patients treated for these approved indications.[3–5] Although persistent B-cell depletion is desired in NHL, it remains unclear whether this is safe or necessary for sustained clinical efficacy in inflammatory diseases.[1,6]

We report an open-label, proof-of-concept investigation of low-dose rituximab in relapsing-type MS. Since July 2008, 12 patients refractory to conventional disease-modifying therapies (interferon and/or glatiramer acetate, and natalizumab) were pretreated with methylprednisolone 500 mg intravenously followed by a 100 mg infusion of rituximab. Repeat infusion could occur at 6-month intervals per the treating neurologist. Forty-four infusions were administered to 12 patients over 283 patient-months of follow-up. We observed a near complete reduction of CD19+ lymphocytes (0–0.6%) at 2 weeks, and this effect persisted for a period of 6 weeks (0–0.5%). Return of more than 25% of baseline CD19+ lymphocytes was observed in 3 patients (27%) at 12 weeks and 5 patients (45%) at 24 weeks. Our cohort experienced a combined total of 21 clinical relapses in the year prior to first infusion and 7 relapses in the year following. Baseline cumulative gadolinium-enhanced lesions on cranial MRI totaled 23, which improved to 3, 2, and 0 at weeks 12, 24, and 52, respectively. At Beth Israel Deaconess, 7 patients have continued on this protocol after the first year of treatment and all have experienced complete cessation of relapses and MRI disease activity with continued follow-up (mean $\pm$ SD of 30.9 $\pm$ 3 months). To date, there have been no infusion reactions. Two adverse events were reported: an uncomplicated urinary tract infection and a case of oral thrush during treatment of a relapse with intravenous methylprednisolone 5 weeks after rituximab.

Despite the FDA's expectation for industry to identify the minimally effective dose, the clinical-therapeutic paradigm of complete and persistent B-cell depletion using high-dose anti-CD20 biologics has not been challenged previously by industry-initiated studies.[7] Our data suggests that a single 100-mg infusion of rituximab adequately depletes peripheral B cells for at least 6 weeks and is well tolerated. Although our proof-of-concept design is not adequate to drawn firm conclusions regarding clinical efficacy measures, the improvement in clinical and radiographic metrics calls into question whether sustained B-cell depletion is necessary to maintain the clinical effects of rituximab in the treatment of relapsing forms of MS. Our results underscore the need for future clinical investigations to determine the minimally effective—and potentially safer—dose of rituximab.

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