Treatment of Refractory Anti-HMG-CoA Reductase Myopathy: A Role for Rituximab?

Anti-hydroxymethylglutaryl CoA reductase (HMGCR) myopathy is a subtype of myositis characterized by proximal muscle weakness, elevated serum creatine kinase (CK) levels, and autoantibodies recognizing HMGCR¹. While statins are an established risk factor for developing anti-HMGCR myopathy in older patients, some individuals develop this condition without a known statin exposure^{2,3}. To date, effective treatment strategies have not been established in clinical trials. Nonetheless, many patients with anti-HMGCR myopathy improve with immunosuppressive therapy, and current expert opinion guidelines recommend initiating treatment with corticosteroids, methotrexate, and/or intravenous immunoglobulin (IVIG)¹. Unfortunately, a significant number of patients with anti-HMGCR myopathy have persistently active disease despite aggressive treatment with these and other agents. Indeed, a study including 50 patients with anti-HMGCR myopathy treated for 2 years or more found that 30% continued to have weakness and elevated muscle enzymes⁴. This underscores the importance of finding more effective treatment modalities for these patients.

A number of observations suggest the possibility that autoantibodies may play a pathogenic role in anti-HMGCR myopathy. For example, anti-HMGCR titers have been shown to correlate with disease activity⁴. In addition, muscle biopsies from patients with anti-HMGCR myopathy reveal membrane attack complex deposited on the surface of muscle fibers⁵. Further, anti-HMGCR autoantibodies not only cause atrophy of cultured human myotubes⁶, but they also lead to myofiber necrosis (albeit limited) and muscle weakness when injected into mice⁷. Given the possibility that anti-HMGCR autoantibodies may be pathogenic and given the prominent role played by B cells in autoantibody production, B cell depletion would appear to be an effective treatment strategy for anti-HMGCR myopathy.

In this issue of *The Journal*, Landon-Cardinal, *et al*⁸ report on the outcomes of 9 patients with anti-HMGCR myopathy who were treated with rituximab (RTX), a chimeric

monoclonal antibody targeting CD20+ B cells. These patients had disease durations ranging from 0.75 to 23 years and refractory disease despite prior treatment with 1 or more agents, often including IVIG. While 6 of these patients had no clear improvement with RTX, 3 had a positive response defined by (1) a reduction of CK levels to less than twice the upper limit of normal and/or resolution of T2/ short-tau inversion recovery hyperintensities on magnetic resonance imaging (MRI), (2) no worsening of proximal muscle strength, and (3) the tapering of corticosteroids to < 15 mg per day and the discontinuation of IVIG. None of the RTX responders had a known statin exposure.

Along with a previously published case series reporting improvement in 2 out of 5 patients with anti-HMGCR myopathy treated with RTX⁹, the current study provides additional evidence that B cell depletion may be effective in patients with refractory disease. However, several observations may limit optimism about the efficacy of RTX in the patients described by Landon-Cardinal and colleagues⁸. The first responder was simultaneously treated with prednisone, IVIG, and cyclophosphamide, making it difficult to assess whether RTX was responsible for the improvement. The second and third responders had disease for more than 10 years and were severely weak with normal CK levels prior to RTX therapy. Because high CK levels are usually associated with disease activity in anti-HMGCR myopathy, these 2 patients either had relatively inactive disease or extensive fatty replacement of muscle tissue that prevented an elevated CK level. In the second responder, a change in strength from 2 to 3 out of 5 on the Medical Research Council strength scale was the sole indicator of response. The third responder had no change in strength or CK levels with RTX, and only the resolution of muscle edema on MRI suggested any response to the treatment. While a modest improvement in strength and the resolution of edema on MRI are encouraging, one would hope to see more robust evidence of treatment response before concluding with certainty that RTX is an effective therapy for some patients

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with anti-HMGCR myopathy. Such evidence will most likely emerge only from a well-designed clinical trial of RTX in this patient population.

The limitations of this retrospective case series notwithstanding, the observations of Landon-Cardinal, *et al*⁸ suggest that RTX could be considered as a rescue therapy in patients with refractory anti-HMGCR myopathy. Assuming some patients with anti-HMGCR myopathy do respond to RTX, the study also raises questions. If given earlier, could RTX have prevented the extensive chronic muscle damage presumably experienced by 2 of the responders? How many other agents should be tried and for how long before resorting to RTX? Why do only some patients seem to respond to RTX? What treatments should we offer the majority of patients with refractory anti-HMGCR myopathy who do not respond to RTX, IVIG, and other conventional immunosuppressive medications? Given the deposition of membrane attack complex on the surface of myofibers, could inhibitors of the terminal complement pathway be considered as a possible treatment option? These are pressing questions for the one-third of patients with anti-HMGCR myopathy who currently have a chronic progressive myopathic process despite aggressive immunosuppressive therapy.

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