

Rituximab use for refractory anti-HMGCR immune-mediated necrotizing myopathy: A case report

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SUMMARY Immunosuppression is the cornerstone therapy for anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) myopathy. Typical immunosuppressants such as corticosteroids, methotrexate, and azathioprine have been used in conjunction with removal of the offending agent, yet the use of rituximab is more limited in this type of myopathy. Reported here is a case of a patient who responded well to rituximab (RTX) after the standard immunosuppressants had failed. This case illustrates the importance of further studies to evaluate the role of RTX in anti-HMGCR myopathy.

Keywords anti-HMGCR, immune-mediated necrotizing myopathy, immunosuppressants, rituximab

1. Introduction

Immune-mediated necrotizing myopathy (IMNM) is an autoimmune condition resulting from the direct or indirect injury of myofibers by the immune system. Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) myopathy is a subtype of IMNM and was first described in 2010 (1). It has been seen both in statin-naïve and statin-exposed patients, with a prevalence of 1-2 cases per million in those who are statin-exposed (2). It presents with muscle weakness, myalgia, and elevated serum creatine phosphokinase with a mean age of 55 years. Studies have found that statin-naïve patients were younger than statin-exposed patients (3). There are currently no guidelines for the management of anti-HMGCR myopathy. Immunosuppressants are the cornerstone of therapy, but very few studies regarding the use of rituximab (RTX) have been published - all with varying responses (4). Described here is a case of anti-HMGCR-associated IMNM refractory to conventional immunosuppressants but responsive to RTX.

2. Case Report

A 61-year-old female with a history of primary hypercholesterolemia, hypothyroidism, and hypertension presented with rapidly progressing proximal upper and lower muscle extremity weakness for seven days. Her symptoms were associated with muscle pain and slowly progressive dysphagia to both solids and liquids. Her medication history included taking pravastatin for two

years. A physical examination revealed a grade of 3/5 on the Medical Research Council (MRC) Scale for Muscle Strength in the proximal upper and lower extremities bilaterally. Laboratory tests including a complete blood count, renal function test, and inflammatory markers (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) were normal. Her creatinine kinase level was 15,000 U/L (normal, 26-192 U/L), her myoglobin level was higher than 1,000 (normal, 9-83ng/mL), and aspartate aminotransferase (309 U/L; normal: 10-40 U/L) and alanine aminotransferase (691 U/L; normal: 12-78 U/L) were elevated (Table 1). Differentials were polymyositis, statin-induced myopathy, paraneoplastic myopathy, and anti-signal recognition particle-associated myopathy.

Liver ultrasound was normal. Statin was discontinued and oral prednisone at a dose of 60 mg was started since IMNM was suspected. An initial rheumatologic work-up for autoimmune myopathies was negative including rheumatoid factor, antinuclear antibody, and anti-myositis antibodies including anti Jo1, anti Ro, anti-signal recognition particle, anti-mi-2, acetylcholine receptor antibody, and muscle-specific tyrosine kinase antibody. Pan computed tomography including the chest, abdomen, and pelvis did not reveal evidence of a malignancy. Magnetic resonance imaging of the right lower extremity revealed diffuse patchy muscular atrophy throughout the thigh with extensive patchy muscle edema involving the anterior medial and posterior compartments. The right quadriceps was biopsied, an electromyogram and anti-HMGCR antibodies were ordered, and pending biopsy results the patient was discharged on 60 mg of steroids.

Table 1. Laboratory results from the initial visit and subsequent visits

Laboratory tests	Normal reference values	On admission	28 days On the steroid azathioprine	42 days Azathioprine discontinued and rituximab initiated	56 days	84 days	112 days	168 days	365 days
C-Reactive Protein	≤ 9 mg/L	< 2.90	< 2.90						
Creatinine Kinase	26-192 U/L	15,000	2,040	1,300	989	837	132	114	96
Aspartate Aminotransferase	10-40 U/L	309	86		47	29	20	20	
Alanine Aminotransferase	12-78 U/L	691	447		151	49	38	36	
Total Bilirubin	0-1.5 mg/dL	0.4	0.4		0.6	0.4	0.4	0.3	
Myoglobin	9-83 ng/mL	> 1000							
Thyroid-stimulating Hormone	0.4-5 uIU/mL	2.124			2.330				
Carcinoembryonic Antigen		Negative							
Myositis-specific Antibodies		Negative							
CA-19-9		Negative							
CA 125		Negative							
Rheumatoid Factor	< 15 IU/mL	< 10							
Antinuclear Antibody		Negative							
Aldolase	1.5-8 U/L	135	63.6		6.1				

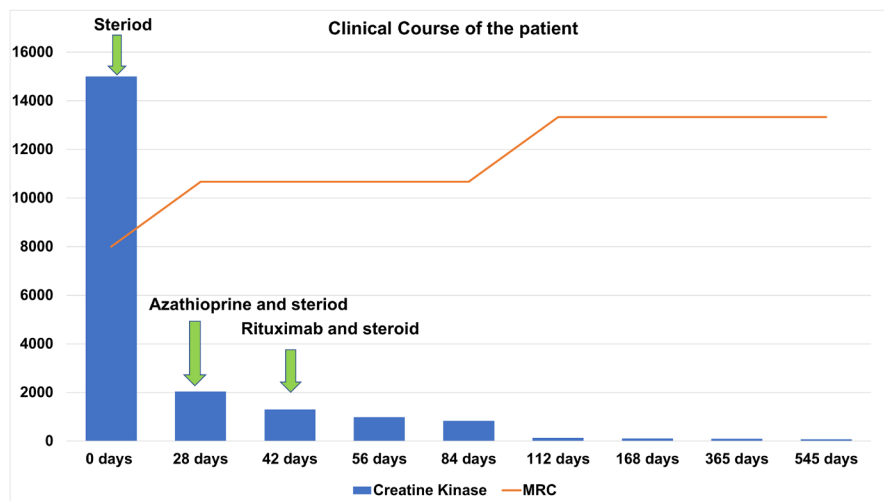


Figure 1. Clinical course after rituximab was initiated and muscle strength recovered to the baseline level after 3 months of rituximab therapy: CK levels and muscle strength on the MRC scale (data points). Less muscle strength in the hip flexors was noted on admission according to the MRC scale.

During her 4-week follow up in the rheumatology clinic, she was still complaining of weakness. Her upper arms and bilateral hip flexors were MHC grade 4/5. Her repeat creatine kinase (CK) level was around 2,000 U/L. The quadriceps biopsy revealed scattered myofiber atrophy, degeneration, regeneration, necrosis, and myophagocytosis suggestive of necrotizing myopathy. Electromyography (EMG) was performed and revealed myositis, and anti-HMG CoA reductase antibodies were positive, with a titer of 99 (normal < 20 units) suggestive of anti-HMGCR-induced myopathy. The patient was subsequently started on azathioprine (AZA) 50 mg daily.

Fifteen days later, patient complained of nausea and did not want to continue taking AZA. She still had weakness in her upper extremities. Her aspartate aminotransferase level was 82 U/L, her alanine aminotransferase level was 269 U/L, and her CK level

was 1,300 U/L. The steroid dose was decreased to 30 mg, AZA was stopped, and a plan was formulated to start the patient on an RTX intravenous infusion 1,000 mg/m² with a second dose repeated 2 weeks later. Four weeks after RTX was initiated, her strength improved in her shoulders, fingers and toes, and proximal hip flexors. Her RTX dosage was then decreased to 375 mg/mm² given once every 3 months. Remission was deemed to have been achieved after six doses of RTX since the patient's CK level and aldolase level were consistently normal and she was asymptomatic. The patient was also started on alirocumab for hyperlipidemia. The patient responded well to RTX within 4 weeks of treatment initiation and went into complete remission within 3 months of initiation of RTX, with normal CK levels and no relapse (Figure 1). She subsequently tolerated her maintenance therapy for one year with no complications. She is currently symptom-free.

3. Discussion

Anti-HMGCR myopathy is a rare subtype of severe necrotizing autoimmune myopathy (5-7). There are few prospective studies and clinical trials in the literature to guide therapy for this specific myopathy. The regimen mainly depends on disease severity and a discussion between the rheumatologist and the patient. Prompt discontinuation of statin therapy and immunosuppressants are the initial treatment for statin-induced IMNM. Common immunosuppressive that have been shown to be effective are corticosteroids, intravenous immunoglobulin (IVIG), AZA, methotrexate (MTX), and mycophenolate mofetil (5,9,10). MTX or IVIG have been used for refractory cases, with both resulting in improvement (3,10-12). The postulated mechanism for anti-HMGCR myopathy includes autoimmunity against HMGCR; since B cells play a big role in autoantibody production, B cell depletion would appear to be an effective treatment strategy for the condition (2). Experience with RTX is limited. In 2016, the European Neuromuscular Centre (ENMC) convened a workshop on the definition and treatment of IMNM for anti-HMGCR myopathy. The experts reached the consensus that patients with anti-HMGCR myopathy should be treated with both corticosteroids as well as a second-line agent either immediately or within 1 month of presentation, depending on the severity of disease and the response to steroid treatment. They suggested RTX as a possible alternative and indicated that it could be combined with MTX in severe cases (13).

There are very few studies on RTX response in refractory anti-HMGCR IMNM. Landon-Cardinal *et al.* conducted a retrospective study in which 9 out of 46 patients with anti-HMGCR IMNM received RTX after failing to respond to an average of three other immunosuppressants. All patients presented with proximal muscle weakness and a mean CK level 1,602 IU/L prior to RTX. Three out of nine patients on RTX had improved muscle strength and improved MRI findings. The most striking effect of RTX was seen in two statin-naïve younger patients, and the response was seen in the first month after starting the therapy. RTX was also helpful in weaning two patients off of corticosteroids and IVIG medication. All three patients were in remission prior to the last follow up. One patient who received RTX early in the course of the disease did not respond even after five months of treatment but was then successfully treated with CS, IVIG, and AZA (4).

Ashton *et al.* (14) described a case series of twenty patients with anti-HMGCR myopathy and a mean initial CK level of 7,189 U/L. RTX was initiated in five patients who failed to respond to prednisolone, MTX, AZA, and IVIG. Improvement was seen in two patients treated with RTX. Those two patients were also statin-

naïve younger patients, so results were similar to those reported by Landon-Cardinal *et al.* (4). There are a few other case series in which RTX was used to treat patients with refractory anti-HMGCR but it resulted in no benefit (10,15).

The current patient improved slightly with oral steroids and according to tests but did not go into remission. AZA was used for few days and was stopped due to adverse reactions. RTX was ultimately started. The patient started responding within one month of treatment and went into complete remission within 3 months of initiation of RTX, with normal CK levels and a normal MRC grade; the patient has not relapsed.

4. Conclusion

RTX was effective in the current patient with refractory anti-HMGCR myopathy. The patient's response to RTX leads to questions like why statin-naïve patients respond better, why it does not beneficial all the patients if autoimmunity is the cause, and whether RTX can be used in the initial course of disease to minimize that course. In addition to a few cases reported in the literature, the current case highlights the need for a prospective randomized trial to confirm the effectiveness of RTX in anti-HMGCR myopathy.

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