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## Complete remission induced by rituximab in refractory, seronegative, muscle-specific, kinase-positive myasthenia gravis

Rituximab is a chimeric IgG1  $\kappa$  monoclonal antibody that targets CD20, a transmembrane phosphoprotein on most B cells. Rituximab depletes B cells by binding to the CD20 molecule and initiating complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity.<sup>1</sup>

Recently, there was a case of muscle-specific kinase (MuSK)-positive myasthenia gravis (MG) successfully treated with rituximab.<sup>2</sup>

We report a patient with MuSK-positive generalised MG who achieved complete remission with rituximab, after being refractory to steroids, intravenous immunoglobulin, immunosuppressants, thymectomy and less responsive to plasmapheresis.

A 32-year-old man was referred for refractory MG. He gave a 2.5-year history of mild bulbar and generalised weakness, mostly in proximal extremities, without sensory symptoms. He denied ptosis and diplopia but reported mild dysphagia and dysarthria. Family history was negative for neuromuscular disorders. He was receiving no medications. He denied any history of smoking and drank socially.

The general physical examination was unremarkable. Neurological examination demonstrated diplopia on extreme lateral gaze without fatigable ptosis or Cogan's lid twitch sign. There was moderate weakness of facial muscles bilaterally and of the tongue, without atrophy. He had mild dysarthria without voice fatigue and mild proximal limb weakness with sustained shoulder abduction for 10 s. No neck weakness was detected. He could perform 10 squats without difficulty. Sensation, gait, coordination and deep tendon reflexes were

all normal except for mild hyporeflexia at the ankles. Plantar responses were flexor.

Initial investigations elsewhere included baseline 2 Hz repetitive nerve stimulation with decremental responses of 17% at the right median and 66% at the right musculocutaneous nerves without post-exercise facilitation, a negative Tensilon test with simultaneous measurement of forearm and grip strength, and repetitive nerve stimulation of the median nerve 2 h before and 2 days after 120 mg of Mestinon, and a negative acetylcholine-receptor antibody panel. A muscle biopsy did not show any myopathic features.

His symptoms had not responded to a 1-month trial of pyridostigmine at maximal doses of 240 mg/day. Prednisone at 60–80 mg/day for 2 years had been ineffective. A thymectomy had been performed 2 years before, which revealed thymic hyperplasia, but he had failed to improve. Azathioprine caused hepatotoxicity with jaundice. His condition deteriorated and he developed profound, mainly proximal upper and lower limb weakness. The only beneficial treatment was plasmapheresis, and he eventually obtained good control with three exchanges per week, alternating with two exchanges per week. Plasmapheresis was suspended briefly to try intravenous immunoglobulin 2 g/kg, but his condition worsened dramatically, and plasmapheresis was re-started.

Ciclosporin (150–200 mg twice daily) was added to reduce his condition and to reduce his dependence on plasmapheresis, with some success. At times he had no limb weakness, but the moderate to severe facial and tongue weakness did not change. After 5 years, his condition began to deteriorate slowly, becoming less responsive to plasmapheresis, and he became continuously weak. Mycophenolate mofetil (1000 mg twice daily) was added for 3 months, but without success. A 6-month trial of cyclophosphamide IV, 1 g/m<sup>2</sup> surface area every month, also provided no benefit.

When the assay became commercially available, MuSK antibodies were found; titres were not measured. A repeat CT showed no residual thymic tissue. His condition continued to decline despite plasmapheresis three times a week, and so treatment with rituximab was started 3 months after his last dose of cyclophosphamide. He received four doses of rituximab 375 mg/m<sup>2</sup> every week for two cycles and noted improvement of his symptoms after the first cycle. After that, he received one infusion every 10 weeks. After several months, he was able to discontinue plasmapheresis, and has remained off all other medications for 1.5 years. Rituximab infusions were stopped 6 months ago after 1 year of treatment and he remains in complete remission. MuSK antibodies have not been checked for again because of insurance restrictions.

A chimeric murine/human IgG1  $\kappa$  monoclonal antibody against CD20, rituximab depletes B cells by binding to the CD20 molecule and initiating complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity,<sup>1</sup> hence providing therapeutic benefit for many B cell-mediated diseases. Rituximab is a Food and Drug Administration-approved drug for the treatment of relapsing/refractory CD20-positive low-grade non-Hodgkin's lymphoma. Rituximab has been used successfully with other autoimmune neuromuscular diseases. Side effects include severe or fatal infusion reactions, infections, hypersensitivity, cardiac

arrhythmias, renal toxicity, bowel obstruction and perforation.

Previous reports have described refractory generalised seropositive MG responding serendipitously to rituximab when MG arose in association with bone marrow transplantation or with lymphoma.<sup>3–5</sup> Recently, there was a report of a 56-year-old woman with bulbar MuSK-positive MG refractory to prednisone, azathioprine and mycophenolate mofetil, but less responsive to plasmapheresis, who had improved with 2 months of rituximab treatment. She has been stable for 12 months, but needed to be re-treated with Mestinon and mycophenolate mofetil 1000 mg/day, 3 months after the first rituximab course.<sup>2</sup> Ours is the second case of isolated refractory seronegative, MuSK-positive MG achieving complete remission after receiving rituximab, and the first case to achieve and maintain this for over 1.5 years. Rituximab provides more selectivity in targeting B cells compared with immunosuppressants such as ciclosporin, azathioprine and mycophenolate mofetil, which makes this an attractive treatment choice for MG. Rituximab should be considered as a treatment option in MuSK-positive MG refractory to other immunomodulatory agents.

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## Aggravation of ataxia due to acetazolamide induced hyperammonaemia in episodic ataxia

Acetazolamide has been used to reduce the number of attacks in patients with episodic ataxia type 2 (EA 2), presumably by inhibiting