Rituximab Treatment in Myasthaenia Gravis
Report of two paediatric cases

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Myasthaenia Gravis (MG) is an autoimmune disease involving the postsynaptic receptors in the neuromuscular junction. The condition is characterised by fatigable weakness of the skeletal muscles and is uncommon in children. Acetylcholinesterase inhibitors and immune-modifying medications are usually considered the mainstay of treatment. However, these medications have to be given on a lifelong basis so that patients remain in remission; furthermore, drug-related side-effects can have a major impact on quality of life. We report two paediatric cases who were treated for MG at the Sultan Qaboos University Hospital, Muscat, Oman, in 2007 and 2008, respectively. Rituximab was eventually administered to each patient after their condition failed to improve despite several years of standard treatment with acetylcholinesterase inhibitors and immune-modifying medications. Overall, rituximab resulted in complete remission in one case and significant clinical improvement in the other case.

Keywords: Myasthenia Gravis; Rituximab; Children; Cholinergic Receptors; Case Report; Oman.

Case One

A seven-year-old female patient presented to SQUH in 2007 and was diagnosed with MG. She was prescribed prednisolone, pyridostigmine and azathioprine and underwent a thymectomy in 2009. Her acetylcholine receptor (AchR) antibody levels were 85,000 nmol/L in 2007 and 292 nmol/L in 2013 (normal range: 0–0.25 nmol/L). An anti-muscle-specific kinase (MuSK) antibody test was not performed. For several years, she continued taking pyridostigmine, prednisolone and azathioprine; however, she still had minimal ptosis and was easily fatigued. She could not participate in active games and, according to the Myasthenia Gravis Foundation of America (MGFA) scale, her muscular weakness was categorised as class IVa. The patient was the elder sister of another previously reported female child with MG.

In 2012, five years after her initial MG diagnosis, the patient was prescribed rituximab. Although she
Rituximab treatment was initiated in 2014, more than five years after her initial MG diagnosis. Clinical improvement was evident after the second dose. After three months, once all four doses of rituximab had been administered, prednisolone was tapered off and all other drugs were discontinued, including the azathioprine, pyridostigmine and atenolol. At the time of writing, the patient had been asymptomatic for two years. She was given one additional dose of rituximab in 2016 after her CD19 count had normalised.

A summary of the clinical characteristics and management plans of both cases is shown in Table 1.

**Table 1: Clinical characteristics and management plans of two paediatric cases of myasthenia gravis treated with rituximab**

<table>
<thead>
<tr>
<th>Case one</th>
<th>Case two</th>
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</thead>
<tbody>
<tr>
<td><strong>Age at MG onset in years</strong></td>
<td>7</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Female</td>
</tr>
<tr>
<td><strong>Year of presentation</strong></td>
<td>2007</td>
</tr>
<tr>
<td><strong>MG severity</strong></td>
<td>IVa</td>
</tr>
<tr>
<td><strong>Initial treatment</strong></td>
<td>PRD, PYD, IVIGs and AZA</td>
</tr>
<tr>
<td><strong>Number of MG crises</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Thymectomy</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>AchRab status</strong></td>
<td>Positive†</td>
</tr>
<tr>
<td><strong>Rituximab dosage</strong></td>
<td>Four doses of 375 mg/m²</td>
</tr>
<tr>
<td><strong>Response to treatment</strong></td>
<td>After the fourth dose</td>
</tr>
<tr>
<td><strong>Number of cycles</strong></td>
<td>1 full cycle</td>
</tr>
<tr>
<td><strong>Current treatment</strong></td>
<td>PRD, PYD and AZA</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Significant clinical improvement</td>
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*MG = myasthenia gravis; PRD = prednisolone; PYD = pyridostigmine; IVIGs = intravenous immunoglobulins; AZA = azathioprine; AchRab = acetylcholine receptor antibody.

†Initially, her AchRab levels were 85,000 nmol/L in 2007 before dropping to 292 nmol/L in 2013.

Rituximab is an anti-B-cell CD20 monoclonal antibody used in the treatment of several autoimmune neurological disorders, including neuromyelitis optica, opsoclonus ataxia syndrome, and autoimmune neuro-ophathies.²² The drug was first used for the treatment of MG in 2003.²² Since then, several reports have been published indicating a good clinical response to the drug.²² In a recent systematic review, Tandan et al. reported that 71% of MG patients have shown improvement with rituximab therapy.²² Currently, a multi-centre phase II rituximab trial is being undertaken among MG patients in the USA, with preliminary results to be reported soon.²² In a 10-year open-label study, rituximab was well-tolerated, resulting in sustained clinical improvement and the eventual tapering off of other immune therapies.²²

Although the majority of MG cases demonstrate an effective and sustained response with rituximab with few complications, the potential adverse effects of the drug should be considered prior to treatment.²² Rituximab can cause serious side-effects, including progressive multifocal leukoencephalopathy, the reactivation of dormant hepatitis and epidermal necrolysis.²² However, as the current cases were asymptomatic, they were not screened for these side-effects.

In the first case, the patient was the elder sister of another previously reported female child with class V MG who presented to SQUH in 2012 at the age of four years.²² The younger sister was prescribed incremental doses of prednisolone and pyridostigmine, but her features and osteopaenia with reduced bone density requiring vitamin D therapy. She was on regular monthly IVIG therapy (1 g/kg). A thymectomy was advised but not performed, as her father did not consent to the procedure. According to the MGFA scale, her muscular weakness was categorised as class IVb.²²

As the patient’s symptoms did not improve, rituximab treatment was initiated in 2014, more than five years after her initial MG diagnosis. Clinical improvement was evident after the second dose. After three months, once all four doses of rituximab had been administered, prednisolone was tapered off and all other drugs were discontinued, including the azathioprine, pyridostigmine and atenolol. At the time of writing, the patient had been asymptomatic for two years. She was given one additional dose of rituximab in 2016 after her CD19 count had normalised.

A summary of the clinical characteristics and management plans of both cases is shown in Table 1.

**Case Two**

A five-year-old girl presented to SQUH in 2008 with ptosis, difficulty swallowing and mild generalised weakness. Clinical investigations confirmed a diagnosis of MG. The results of AchR antibody tests performed in 2008 and 2013 were negative. An anti-MuSK antibody test was not performed. She was prescribed pyridostigmine, 2 mg/kg/day of prednisolone, azathioprine and atenolol (due to steroid-related hypertension). She also developed severe Cushingoid features and osteopaenia with reduced bone density requiring vitamin D therapy. She was on regular monthly IVIG therapy (1 g/kg). A thymectomy was advised but not performed, as her father did not consent to the procedure. According to the MGFA scale, her muscular weakness was categorised as class IVb.²²
condition progressively worsened over time and she was intubated six times. Further investigation revealed that her CD19 count was persistently elevated, with occasional fluctuations. After several months, her CD19 count normalised and she remained asymptomatic for 20 months; however, she subsequently relapsed and underwent a second cycle of rituximab treatment.

At present, there are no indicators other than CD19 count to guide rituximab use following the first round of treatment. Although the CD19 count is initially suppressed by rituximab, it normalises once the effect of the drug wears off. Rituximab treatment should therefore be repeated once the CD19 count normalises to avoid clinical relapse. In the second case, the rituximab dose was repeated once the patient’s CD19 count had normalised, before the recurrence of any clinical weakness. For the first case, additional measures were taken to prevent further relapse.

Table 2: Standard protocols for paediatric rituximab treatment at the Sultan Qaboos University Hospital, Muscat, Oman

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Details</th>
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<tbody>
<tr>
<td>Dosage</td>
<td>375 mg/m² once weekly for four weeks, with subsequent doses depending on the patient’s initial response to treatment.</td>
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</tbody>
</table>
| Dilution          | Add a solution of 0.9% sodium chloride or 5% glucose for a final concentration of 1–4 mg/mL.  
|                   | Mix gently to avoid foaming.                                           |
| Pre-treatment     | The following medications should be administered orally 30–60 minutes prior to each infusion:  
|                   | a) 15 mg/kg of paracetamol (up to a maximum of 1 g)  
|                   | b) Chlorpheniramine at dosages of:  
|                   | (i) 1 mg twice for patients between 1 month and 2 years old  
|                   | (ii) 1 mg every four to six hours for patients between 2–6 years old  
|                   | (iii) 2 mg every four to six hours for patients between 6–12 years old  
|                   | (iv) 4 mg every four to six hours for patients between 12–18 years old.  |
|                   | Intravenous corticosteroids may also be given if required (e.g. two doses of 0.1 mg/kg of dexamethasone).  
|                   | Consider withholding antihypertensive medications for 24 hours to prevent hypotension.  
|                   | Screen for hepatitis B before starting rituximab, as this treatment can reactivate dormant infections.  
|                   | For patients with pre-existing pulmonary disease, concomitant nebulised salbutamol should be considered. |
| Administration    | The drug should be infused over an 8-hour period at an initial rate of 10 mL/hour, before increasing to 15 mL/hour, 20 mL/hour, 30 mL/hour and 40 mL/hour for half-hour intervals each. The infusion rate should then be maintained at 50 mL/hour until the entire dose has been administered.  
| Compatibility     | Apart from 0.9% sodium chloride and 5% glucose, rituximab should not be mixed with any other fluids or drugs.  
|                   | The catheter should be flushed with saline or glucose before and after the rituximab infusion. |
| Potential adverse effects | Fever and chills/rigors may occur in up to 50% of patients.  
|                   | Infusion-related symptoms include nausea, vomiting, urticaria, headaches, bronchospasms, dyspnoea, angioedema and hypotension.  
|                   | Severe gastrointestinal adverse effects including obstruction and perforation have been reported; complaints of abdominal pain, especially early in the treatment course, should be investigated.  
|                   | Patients with pre-existing pulmonary disease may be at greater risk of respiratory adverse effects.  
|                   | Rituximab can exacerbate or induce arrhythmias or angina.  
|                   | Adverse reactions are usually more severe during the first infusion; however, anaphylaxis can occur at any time and at any stage of treatment.  
|                   | In case of anaphylaxis, emergency treatment (i.e. adrenaline and corticosteroids) should be readily available. |
| Observation and monitoring | The patient’s vital signs and the site of the infusion should be checked every 15 minutes during the first hour of the infusion, then every hour until the infusion is complete.  
|                   | Routine observation should continue at 30-minute intervals for two hours following the completion of the infusion in order to monitor any delayed reactions.  
|                   | The infusion should be halted immediately if any adverse effects arise; if the effects are mild and the symptoms resolve, the infusion may be restarted at half the previous rate of infusion.  
|                   | Cardiac monitoring may be required for patients with cardiac dysfunction.  
|                   | Continue to monitor patients for signs of hepatitis B infection during and for several months after treatment; rituximab must be discontinued if fulminant hepatitis develops.  
| Follow-up         | A complete blood count, including differential and platelet counts, should be obtained at weekly intervals for inpatients and fortnightly intervals for outpatients.  
|                   | Lymphocyte subset panels should be undertaken every three months.  
|                   | Urea and electrolyte levels should be monitored on a daily basis for inpatients and prior to every infusion for outpatients.  

Rituximab was thus administered to the first case in light of the successful outcome achieved for her younger sister.
the CD19 count remained suppressed and had still not reached normal values more than four years after the initial rituximab treatment. The duration of the period of CD19 suppression is variable.\(^9\) In this case, the patient was asymptomatic and hence was not screened for progressive multifocal leukoencephalopathy or a John Cunningham virus infection.

Tandan et al. noted that rituximab resulted in a better response among patients with anti-MuSK antibodies compared to those with anti-AChR antibodies.\(^6\) In the current report, the second patient was negative for AChR antibodies and seemed to respond most positively to the rituximab treatment. The first patient had positive AChR antibody test results, which, despite a significant decline between 2007 and 2013, never normalised; furthermore, this patient did not respond as well to rituximab treatment as the AChR antibody-negative patient. Negative AChR antibody test results may therefore be a good marker for predicting remission with rituximab treatment. However, it is important to note that AChR antibody levels appear to increase with age and that cases of childhood-onset MG may initially appear to be AChR antibody-negative.\(^7\)

It is not yet clear whether there is any correlation between the duration of MG and the efficacy of rituximab therapy. In the first case, rituximab did not appear to result in the complete resolution of MG symptoms, although the therapy was not initiated until five years after her initial MG diagnosis. Rituximab treatment was also far more effective for her younger sister when administered within a year of the onset of the symptoms.\(^9\) However, the second case also received rituximab after having had MG for five years, resulting in the complete amelioration of her MG symptoms. Future studies may therefore reveal more information in this context.

A thymectomy is often performed as part of MG treatment for adults; however, it is sometimes used in childhood MG as well, the effect of the procedure is slow and takes place over time.\(^10\) In the first case, the patient had undergone a thymectomy seven years prior to rituximab treatment, with seemingly little improvement. As such, the authors suggest that rituximab therapy be considered for pediatric patients with MG from the time of onset of clinical symptoms, except in cases of ocular MG. However, local experience using rituximab is advised. Additionally, the long-term outcomes of rituximab in MG patients with primary disease is unknown. Therefore, the long-term follow-up of such patients is recommended to ensure sustained remission and to monitor for possible side-effects.

**Conclusion**

This report describes two cases of paediatric MG in which the use of rituximab therapy resulted in remission or significant clinical improvement. Rituximab should therefore be considered in similar cases from the time of disease onset. However, the authors highly recommend the continuous follow-up of these patients as the long-term outcome of this treatment has not yet been established.

**ACKNOWLEDGEMENTS**

The SQUH protocols for rituximab therapy in MG cases are adapted from the 2007 and 2009 protocols of the John Hunter Children’s Hospital, Newcastle, New South Wales, Australia, and the Brain Institute at Miami Children’s Hospital, Miami, Florida, USA, respectively.

**References**


