Abstract:

**OBJECTIVES:** Approximately 10%–15% of patients with myasthenia gravis (MG) are refractory to standard treatment. A sizable chunk of these patients is due to muscle-specific tyrosine kinase (MuSK) antibody-positive MG which often runs a severe course with frequent relapses and poor response to conventional treatment. We report six patients with refractory MuSK-positive MG who responded well to the treatment with rituximab.

**PATIENTS AND METHODS:** In this prospective institute-based observational study, we report six MuSK antibody-positive MG patients, who did not achieve remission with standard treatment and were later started on rituximab infusion.

**RESULTS:** There was a significant clinical improvement in all patients after starting rituximab.

**CONCLUSION:** Rituximab is an effective immunomodulatory therapy in MuSK antibody-positive MG patients who are not responding to the standard treatment.

**Keywords:** Muscle-specific tyrosine kinase antibodies, myasthenia, rituximab

Introduction

*Myasthenia gravis* (MG) is an autoimmune antibody-mediated neurological disorder characterized by fatigable weakness of voluntary muscles. Most common antibodies associated with MG are anti-acetylcholine receptor (AChR) antibodies followed by anti-muscle-specific tyrosine kinase (MuSK) antibodies. The clinical course of MuSK antibody-positive MG patients is characterized by a severe disease with severe bulbar symptoms, frequent exacerbations, and less favorable response to the first-line treatment (steroids, azathioprine, mycophenolate, intravenous immunoglobulin [IVIG], or plasmapheresis) as compared to AChR-positive patients. The recent availability of rituximab has raised hopes in the management of these patients. We report our experience with six anti-MuSK antibody-positive MG patients who were refractory to the standard treatment and were later responded well to rituximab.

Patients and Methods

This prospective study was conducted at a tertiary care teaching hospital and referral...
center in Northern India. The details of patients are given below in Table 1. An Institutional Ethics clearance was obtained for the study (INT/IEC/2017/1357) (Reference No.NK/3899/res/640). Rituximab was administered in standard doses of 375 mg/m² weekly for 4 weeks. At follow-up, the next cycle of rituximab was given according to CD19 cell counts done at monthly intervals starting from 6 months. Repeat cycles of rituximab were given once CD19 cell counts were >1% and serum IgG levels were normal.

**Results: Case Series**

**Patient 1**
A 50-year-old gentleman, with no previous comorbidities, presented with difficulty in neck holding, double vision, and ptosis of 2½ year duration. Repetitive nerve stimulation (RNS) and neostigmine test were suggestive of MG. Anti-AChR was negative. The patient was started on steroids, pyridostigmine, and azathioprine. Contrast-enhanced computed tomography (CECT) scan of the chest was normal. He improved symptomatically but never had complete remission. After ½ years, he had worsening of symptoms associated with difficulty in chewing and swallowing, slurring of speech, and breathing difficulty. A diagnosis of myasthenic crisis was made, and the patient was given five cycles of plasma exchange with no improvement in symptoms. Anti-MuSK antibody was positive. He was started on intravenous (IV) rituximab (375 mg/m² weekly for 4 weeks, and the symptoms gradually improved. After 2 weeks of initiation of treatment, the breathing difficulty resolved, and ptosis, diplopia, and neck holding improved after the next 2 months. Steroids and azathioprine were tapered and stopped. He is doing well currently at 24 months of follow-up after three cycles of rituximab and is planned for another cycle.

**Patient 2**
A 23-year-old lady presented with 9-month history of weakness in the neck and limb muscles along with bilateral ptosis. RNS and neostigmine test were suggestive of MG. AChR antibodies were negative. With anticipating an impending crisis, she was given IVIG in a dosage of 2 g/kg. Her symptoms improved and she was discharged on steroids, mycophenolate, and pyridostigmine. Two months later, she started having swallowing difficulty for which she received another course of IVIG (2 g/kg) elsewhere. Mycophenolate and steroids were continued. Five months later, she again had dysphagia and ptosis with progressive shortness of breath. She was given IVIG (2 g/kg) for the third time; mycophenolate was replaced by azathioprine. Anti-MuSK sent now was positive and CECT chest was normal. Again 2 months later, she had ptosis, dysphagia, and hoarseness of voice. This time she was administered five cycles of plasma exchange with only mild improvement. In view of persistent symptoms, rituximab (375 mg/m² weekly for 4 weeks) was given. Her bulbar symptoms improved in 2 weeks, and she started taking oral feeds. She is doing well and is in complete remission at 18-month follow-up after completion of two cycles of rituximab.

**Patient 3**
A 49-year-old lady with MuSK-positive MG, diagnosed outside and treated with steroids, presented with fever, cough, and breathlessness for 2 weeks. Keeping a possibility of community-acquired pneumonia, she was managed with IV antibiotics with which her fever improved, but her dyspnea continued. Myasthenia crisis was considered, and a cycle of IVIG (2 g/kg) followed by IV cyclophosphamide was given with mild improvement. She was continuing monthly IV cyclophosphamide but never attained remission. She was then started on IV rituximab (375 mg/m² weekly for 4 weeks), to which she responded remarkably with complete resolution of respiratory difficulty and other symptoms.

**Patient 4**
A 47-year-old gentleman presented a with 2-year history of bilateral ptosis, diplopia, and bulbar weakness. Neostigmine test and RNS were positive, while CECT of the chest was normal. Anti-AChR antibody was negative. Symptoms responded to steroids, pyridostigmine, and azathioprine. He was well for the next 2 years when he had developed severe bulbar weakness and respiratory problems.

| Serial number | Age/gender | CT chest | Previous treatment | Rituximab cycles | Rituximab-related side effects | Follow-up period (months) | Current medicines other than rituximab |
|---------------|------------|----------|--------------------|------------------|-------------------------------|--------------------------|-------------------------------------|
| 1             | 50 male    | Normal   | Steroids, AZA, PLEX| 3                | None                          | 24                       | None                                |
| 2             | 23 female  | Normal   | Steroids, IVIG MMF, AZA, PLEX| 2                | None                          | 18                       | None                                |
| 3             | 49 female  | Normal   | Steroids, IVIG, Cyclo| 2                | None                          | 18                       | None                                |
| 4             | 47 male    | Normal   | Steroids, AZA, PLEX| 3                | None                          | 24                       | None                                |
| 5             | 48 male    | Normal   | Steroids, PLEX, IVIG| 2                | None                          | 18                       | None                                |
| 6             | 58 female  | Normal   | Steroids, PLEX, IVIG| 1                | None                          | 8                        | None                                |

CT=Computed tomography, AZA=Azathioprine, MMF=Mycophenolate, PLEX=Plasma exchange, IVIG=Intravenous immunoglobulin, Cyclo=Cyclophosphamide
difficulty. Anti-MuSK was positive, and five cycles of plasma exchange were administered with no response. IV rituximab was then started with good response after two doses, steroids and immunomodulation were tapered, and rituximab was given weekly for 4 weeks every 6 months. He is symptom free on 2-year follow-up.

**Patient 5**
A 48-year-old gentleman, diagnosed as anti-MuSK-positive MG at another center, was on treatment with steroids and pyridostigmine. He presented to our emergency services with shortness of breath. Five cycles of plasma exchange followed by a course of IVIG were given without improvement. He was then given IV rituximab (375 mg/m² weekly for 4 weeks) and he had complete resolution of symptoms. Steroids were tapered and stopped. He is in remission for the past 1½ year and is on intermittent pulses of rituximab.

**Patient 6**
A 58-year-old female presented with a 1-month history of bulbar symptoms in the form of difficulty in swallowing and speaking. Anti-MuSK antibodies were positive. CECT of the chest was normal. She was treated with five cycles of plasma exchange followed by IVIG. She had persistent bulbar weakness after 1 month of the above treatment, so she was administered IV rituximab. She improved remarkably, with almost complete resolution of her bulbar and other symptoms. She is doing well at 8-month follow-up.

**Discussion**

Anti-MuSK antibodies are found in about 7% of all MG patients. It is seen that 40% of individuals with MG who lack detectable serum AChR antibodies can have anti-MuSK antibodies. The two antibodies act at the neuromuscular junction (NMJ) differently, with anti-AChR using complement system to degrade the postsynaptic AChR, while anti-MuSK produces a change in the NMJ without using the complement. The treatment of MG includes standard initial treatment with corticosteroids and steroid-sparing agents such as cyclosporine, azathiopeine, cyclophosphamide, mycophenolate mofetil, methotrexate, tacrolimus, IVIG, and plasma exchange. However, a substantial number of cases remain refractory to the above treatment, and many of these have MuSK antibody-positive MG.

Rituximab is a genetically engineered chimeric mouse/human IgG1-kappa monoclonal immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. It produces a substantial reduction in circulating CD20+ B-cells for up to 6 months after a cycle of infusions and is used as targeted therapy for a number of neoplastic and autoimmune diseases such as non-Hodgkin’s B-cell lymphoma, Wegener’s granulomatosis, rheumatoid arthritis, immune thrombocytopenia, and autoimmune hemolytic disorders. Rituximab has also been used in a number of neurological disorders, and refractory MG is one of them.

In our prospective study, we report significant clinical improvement in MG with rituximab. Refractory here was defined as patients who did not attain remission after two or more immunomodulatory therapies and those patients who periodically required IVIG or plasmapheresis. In a recent review, predictors of positive response to rituximab therapy in MG were MUSK antibody positivity and young age. In the same review, it was observed that 82% of MuSK MG patients showed decreased antibody titer posttreatment with rituximab. Illa et al. and Hain et al. reported a decline in MuSK antibody titers following treatment with rituximab. Lebrun et al. found significant clinical improvement and stoppage of steroids after the treatment with rituximab. Diaz-Manera demonstrated higher rates of disease remission in MuSK-positive patients with rituximab as compared to their AChR-positive counterparts. Two other studies found rituximab to be effective in the treatment of refractory MG patients. Nowak retrospectively reported 14 refractory generalized MG patients (6 AChR+; 8 MuSK+) treated with rituximab and found sustained clinical improvement as well as a reduction of conventional immunotherapies in all patients.

Our case series elaborates the effectiveness of rituximab in anti-MuSK antibody-positive MG. In the absence of well-conducted, randomized, controlled trials, our case series suggest a role for rituximab in the treatment of MuSK-positive MG patients.

In the current study, rituximab was administered in a dose of 375 mg/m² weekly for 4 consecutive weeks which constitutes one cycle. The same cycle was repeated once CD19/CD20 cell counts rose to > 1%. These counts were done at monthly intervals beginning from the 6th month post rituximab administration. Rituximab was well tolerated by all these patients. Common reported adverse effects in the literature include those related to infusions and include fever, chills, hypotension, and dyspnea. There is a potential risk of development of progressive multifocal leukoencephalopathy, along with other infections. Hence, patients should be educated about possibility of infections and followed regularly for any sign of infection. Regarding the cost-effectiveness of therapy, rituximab is cheaper when compared to the standard treatment of myasthenia with IVIG or plasma exchange.
Conclusion

We suggest that rituximab is an effective and safe immunomodulatory therapy in MuSK antibody-positive MG patients who are not responding to the standard treatment. Future well-designed studies will further help in elucidating its role in the management of MG.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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