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Case Report

Maintenance Plasma Exchange Treatment for Muscle Specific Kinase Antibody Positive Myasthenia Gravis Patients

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Abstract *Background*:Anti-muscle specific kinase antibody positive myasthenia gravis (MuSK MG) is often characterized by a relatively severe and progressive course, refractoriness to standard myasthenia gravis (MG) medications, and an increased risk of myasthenic crisis. We report here successful management of three MuSK MG patients using maintenance therapeutic plasma exchange (TPE) treatment for up to 4.5 years. *Materials*: The study was a 5-year retrospective review of all MG patients treated with TPE between 2008 and 2013 at University of Michigan. Inclusion criteria of MuSK MG were positive for anti-MuSK antibodies and a diagnosis of MuSK MG by staff neurologists. Patient data included age, gender, diagnostic testing results, medications, and the dates and response to TPE treatments. *Results*: A total of 153 MG patients underwent at least one course of TPE between 2008 and 2013. A total of 12 patients (7.8%) were positive for anti-MuSK antibodies. Patients were predominantly female (83.3%) and a median age of onset was 46-years old. Three MuSK MG patients were successfully managed with maintenance TPE. *Conclusion*: Maintenance TPE may be an effective option for MuSK MG patients. The key of successful maintenance treatment at our institution has been to tailor the TPE frequency for each individual, and to modify the treatment interval in conjunction with medical management. J. Clin. Apheresis 30:314–319, 2015. © 2014 Wiley Periodicals, Inc.

Key words: maintenance plasma exchange; MuSK; myasthenia gravis

INTRODUCTION

Approximately 80% of patients with myasthenia gravis (MG) have measureable serum antibodies to the acetylcholine receptor (AchR) [1]. Historically, the remaining 20% of patients have been deemed "sero-negative." Recently, additional auto-antibodies to other neuromuscular junction proteins have been discovered in these patients. Examples include antibodies directed against muscle-specific kinase (MuSK) [1], the muscle proteins titin or ryanodine [2], and most recently to lipoprotein receptor-related protein 4 (Lrp4) [3]. Other potential antigenic targets include neural agrin which binds to LRP4 and CoIQ which is a part of acetylcholinesterase complex [4].

MuSK is an important protein for AchR molecule clustering necessary for efficient signal transduction in the neuromuscular junction [4]. Many reports have been published characterizing anti-MuSK antibody (MuSK Ab) and MuSK Ab positive MG (MuSK MG) patients. The prevalence of MuSK Ab in sero-negative MG patients varies from 0 to 70% [1,5–7]. MuSK MG patients are predominantly female and the age of onset of symptoms is usually in the fourth decade of life [7–10]. Compared to anti-AchR positive MG (AchR MG) patients, they tend to have more severe or refractory clinical symptoms, more rapidly progressive course, and an increased risk of myastenic crisis. When treated with acetylcholinesterase inhibitors, these patients seem to have an increased tendency to experience nicotinic and muscarinic side effects such as fasciculations and gastrointestinal symptoms. Three main clinical patterns have been observed in MuSK MG patients [7,9]. One pattern is characterized by marked oculobulbar weakness with facial and tongue atrophy (Type 1). The second pattern shows prominent neck, shoulder, and respiratory involvement but not ocular weakness (Type 2). The third pattern is not distinguishable from AchR MG patients (Type 3). MuSK MG

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patients also differ somewhat in the results of diagnostic testing such as lower diagnostic yield in repetitive nerve stimulation (RNS), frequently abnormal single-fiber electromyography (SFEMG) of cranial nerve-innervated muscles, myopathy-like routine electromyography (EMG), and often normal thymus gland pathology [7–10]. Regarding therapy: they may respond poorly to anticholinesterase treatment, and some do not respond well to intravenous immunoglobulin (IVIG). However, most seem to respond favorably to immunosuppressive therapy and therapeutic plasma exchange (TPE) [7–10].

TPE is frequently employed for all types of myasthenia, with most patients receiving 5–7 TPEs as treatment for a myasthenic flare or crisis. TPE may be especially helpful for MuSK MG patients, since 93% of those patients showed improvement of symptoms after TPE but little effect from IVIG [10]. Although treatment with several different immunosuppressive agents is effective in treatment of MuSK MG, such treatment may have toxic side effects in many patients, or may not be fully effective. In such cases, use of maintenance TPE may be an effective addition to the treatment regimen. We here report our experience with maintenance TPE treatment in three MuSK MG patients and its outcomes to date.

MATERIALS AND METHODS

Study Design

We performed a retrospective investigation of apheresis service records between January 2008 and December 2013 at the University of Michigan Health System (UMHS). A total of 153 MG patients who received TPE were identified. Among them, three patients with MuSK Abs who have received maintenance TPE were identified. All patients consented to participate ASFA rare disease registry and subsequent publications as deidentified participants.

Each patient's age, sex, race, age of onset of MG, symptoms, MuSK Ab test results, EMG result, dates of TPE procedures, and medications were retrieved from the medical record at UMHS. MuSK Ab was tested at Athena Diagnostics (Marlborough, MA).

TPE procedures were performed using either the Cobe Spectra® or Spectra Optia® Apheresis System (TerumoBCT, Lakewood, CO), and one plasma volume was exchanged with 5% albumin in one procedure. The amount of anticoagulant citrate dextrose solution A (ACD-A) was calculated by the apheresis machine using each patient's total blood volume calculated based on sex, height, and weight to meet the set infusion rate of 0.8–1.0 mL/min/liter of total blood volume. About 2.4 mEq Ca^{++} in the form of calcium gluconate or chloride was added to each 500 mL albumin bottle to prevent citrate toxicity symptoms.

RESULTS

In total, 153 MG patients received TPE between January 2008 and December 2013. Of these, 87 patients (56.9%) were female and 66 patients (43.1%) were male. Among them, 12 patients (7.8%) had MuSK Abs, with 10 females (83.3%) and 2 males (16.7%). The age of onset of the symptoms in this group of MuSK-positive patients was from 11- to 66-years old: the second, 3rd and 4th decade in one patient each, 5th decade in five patients, 6th and 7th decade in two patients each. A median age was 46 years old (mean, 44.0 years old). One patient died due to sepsis in 2009. Among these 12 patients, 2 patients have been receiving maintenance TPE and one patient received it until her condition improved markedly due to medications for other disease. These three MuSK MG patients are presented here and the data is summarized in Table I.

Case 1

A 63-year-old female developed progressive dyspnea and dysphonia in 2004 at age 54. As her condition worsened, she developed confusion and lethargy, and she required mechanical ventilation at an outside hospital (OSH) in 2005. Her cardiopulmonary examinations were all negative and she was initially diagnosed with phrenic nerve palsy. Because the phrenic neuropathy was thought to be immune-mediated, she was treated with IVIG. She responded well to IVIG and was back to her normal activities. In 2007, however, she developed worsening dyspnea and fatigue and was transferred to UMHS for further management. She had no focal neurologic deficits on physical examination at that time. Her sleep study showed frequent oxygen desaturations to 67–80% and she required biphasic positive airway pressure (BiPAP) for hypercarbia at night. Electrodiagnostic studies revealed decremental responses up to 18% on RNS and increased jitter on SFEMG was noted. MuSK Ab was reported to be positive subsequently, and diagnosis of MuSK MG was confirmed. Pyridostigmine did not improve her symptoms, but she responded well to IVIG.

Although her clinical symptoms had improved with IVIG, she developed persistent prominent symptoms of facial weakness and fatigueable dysarthria with prolonged speech over time. She also continued to require BiPAP at night. Additional therapy was deemed necessary; therefore, five TPE treatments (twice a week) were performed in June 2009. She responded to TPE well and felt nearly normal after five TPE. She received another five TPE for mildly worsened symptoms in December 2009 and moved on to maintenance TPE every 8 weeks in March 2010. She responded well to TPE every time, however, she had a significant

TABLE I. Summary of Three Cases (as of 31 August, 2014)

	Case 1	Case 2	Case3
Sex	Female	Female	Female
Age (onset/current)	54/63	38/41	43/48
Anti-MuSK Ab[a]	Positive	Positive	Positive
Anti-AchR Ab[b]	Negative	Negative	Negative
EMG			
RNS[c]	• Decrement up to 18%	• Normal	• Mild decrement
SFEMG[d]	• Increased jitter	• Not done	• Not done
Symptoms	• Respiratory failure • Dysarthria • Dysphonia • Fatigue • Mild ptosis	• Respiratory failure • Dysarthria • Dysphonia • Dysphagia • Fatigue • Neck weakness	• Dysarthria • Dysphagia • Ptosis • Diplopia • Upper extremity weakness
Current immunosuppressives	• None	• Prednisone 5 mg • MMF[f] 2.5 g • Pyridostigmine 60 mg	• Cyclosporine 100 mg (for HLH syndrome[e]) • Decadron 0.375 mg (for arthralgia)
Access and issues	Peripheral	Fistula after 3 TPE[g] courses, infection twice	Peripheral
Induction TPE[g]	5 TPE[g] × 2 courses	10, 6, 7, 6 TPE[g]	5 and 3 TPE[g]
Maintenance TPE[g]	Every 3–8 weeks	Every 7–14 days	Every 2–3 weeks
Duration of maintenance TPE[g]	53 months	16 months	43 months
Thymectomy	No	No	No
Current condition	Stable with minimum symptoms	Stable, mild fatigue	Stable, no MG[h] symptoms

[a]Anti-MuSK Ab: anti-muscle specific kinase antibody.
[b]Anti-AchR Ab: anti-acetylcholine receptor antibody.
[c]RNS: repetitive nerve stimulation.
[d]SFEMG: single-fiber electromyography.
[e]HLH syndrome: hemophagocytic lymphohistiocytosis syndrome.
[f]MMF: mycophenolate mofetil.
[g]TPE: therapeutic plasma exchange.
[h]MG: myasthenia gravis.

return in symptoms by 8 weeks. Therefore, interval shortened to 6 weeks in August 2010 and eventually 4 weeks in September 2011. Since then, her symptoms have been stable with slight dysarthria and ptosis at night. The TPE interval is periodically shortened to every 3 weeks due to mild exacerbation of MG symptoms secondary to infection or stress. She has not had diplopia.

Case 2

A 41-year old female was admitted to the hospital with acute respiratory failure and dysphonia, and was diagnosed with MuSK MG in 2011 at age 38. She had been having progressive dysarthria for two years and progressive dysphagia for 6 months prior to presentation to the emergency department at an OSH. She was found to be hypercarbic and started BiPAP and eventually intubated due to declining mental status. Chest X-ray showed left-sided atelectasis and left hemidiaphragmatic elevation. She was transferred to UMHS for further management. EMG was normal and anti-AchR antibody was negative. However, anti-MuSK antibody was positive leading to the diagnosis of MuSK MG. A swallowing study revealed diffuse pharyngeal weakness and failure of epiglottic inversion, deep penetration, and aspiration during swallows, as well as aspiration from residue in between swallows.

She received total 10 TPE treatments; three times a week at the beginning and twice a week after five treatments, along with prednisone 10 mg daily with remarkable improvement of the symptoms. However, her mild dysarthria worsened again in 6 weeks. Therefore, she received eight TPE divided twice a week followed by three weekly TPE with good response. After the third weekly TPE, she developed central catheter-related polymicrobial (Enterobacter cloacae, *Klebsiella pneumonia*, and coagulase negative staph) blood infection leading to pneumonia, and the catheter was removed. Laboratory data on admission showed increased WBC count (13,700/mm3) with increased absolute neutrophil count (12,100/mm3) and decreased

absolute lymphocyte count (300/mm3). She was treated with prednisone 10–15 mg daily, mycophenolate mofetil 2,000–2,500 mg daily, and pyridostigmine as needed at that time.

After she recovered from pneumonia, she gradually developed generalized fatigue, neck weakness, shortness of breath with accessory muscle use on breathing, in addition to mild dysphonia as a baseline in December 2012. Since TPE was the most effective treatment evidenced by her past history, she received seven TPE treatments divided twice a week in December 2012 and January 2013. An arteriovenous fistula was placed on her right forearm and she received six TPE divided twice a week in March 2013. Thereafter, she moved on to weekly maintenance TPE from April 2013. Her symptoms were stable and she could reduce the treatment frequency from once a week to every other week for the last 6 months of 2013. However, she developed symptomatic recurrence some days before each TPE and the TPE interval was shortened to every 10 days in 2014. Then, her fistula failed in April 2014, and she could not receive TPE for more than 1 month. During this time, she developed significant shortness of breath, fatigue, and dysphagia. A central catheter was placed despite her history of catheter-related infection for TPE. She again developed catheter-related sepsis and pulmonary embolism in July 2014; both were successfully treated. She is now receiving maintenance TPE every 7–10 days and is doing well with only mild dysphonia and fatigue as her baseline. She is on prednisone alternating 5 mg and 10 mg daily, mycophenolate mofetil 2,500 mg daily, and pyridostigmine as needed, in addition to BiPAP use during sleep. She has not had ptosis or diplopia. She received another fistula placement in November 2014.

Case 3

A 48-year-old female with progressive ptosis, diplopia, dysarthria, upper extremity weakness, and mild dysphagia was diagnosed with MuSK MG in 2009 at age 43. Anti-AchR antibody was negative and a brain MRI was normal. Electrodiagnostic testing showed a mild decrement with RNS of the right facial nerve, but was otherwise normal. She was begun on pyridostigmine without much improvement, then started prednisone with some improvement. Because she still had dysarthria, dysphagia, diplopia, and neck pain, she received five TPE over 10 days. She experienced remarkable improvement in her symptoms. However, her symptoms worsened in two weeks after the last TPE, and she received additional three TPE divided twice a week. Since she responded well to TPE, maintenance TPE was initiated every other week from January 2010. Her prednisone dose was slowly tapered from 30 mg to 10 mg. The TPE frequency was decreased to every 3 weeks for 2.5 years. However, she experienced shortened symptom free days between each TPE treatment after her prednisone was further tapered to 7.5 mg per day. Because of prednisone-related side effects, frequent TPE was employed rather than increasing the dose of prednisone. The TPE frequency was increased to every other week again from December 2012. She was also on azathioprine 200 mg daily, and pyridostigmine as needed, even though she did not feel substantial benefit from pyridostigmine.

She was relatively stable until she had a right tympanoplasty for a cholesteatoma in August 2013 at an OSH. Because she could not receive TPE locally, her azathioprine dose was increased. She developed cytomegalovirus and parvovirus infections with acute respiratory distress syndrome, hemophagocytic lymphohistiocytosis (HLH syndrome), and multi-organ failure. She was hospitalized for 2 months but responded well on etoposide. She received two TPE treatments during her admission at times when her MG symptoms flared slightly. As she has been treated with higher doses of immunosuppression for the HLH syndrome, her MuSK-MG has become far less symptomatic, and she is not currently requiring TPE. She is currently receiving low dose dexamethasone and cyclosporine 100 mg daily for her HLH syndrome.

DISCUSSION

MuSK MG has been reported to account for a significant part of "sero-negative" MG for over a decade. MuSK Abs are predominantly non-complement fixing IgG4 subclass [11,12] that may interfere with neuromuscular function by several mechanisms. MuSK antibodies may inhibit binding between MuSK and Lrp4 [13], they may suppress the endplate density of MuSK leading to down-regulation of MuSK signaling at the postsynaptic membrane [14], and may also cause presynaptic functional abnormalities leading to decreased Ach release [15]. It is well known that MuSK MG patients have different clinical course compared to AchR MG patients and a different treatment approach may be necessary.

The MuSK MG patients who have received TPE at the UMHS have the following demographic: 83.3% of patients are female and the age of onset was most often in 5th decade, which is similar to many previous reports [7–10]. All three patients treated with maintenance TPE had bulbar symptoms. Cases 1 and 2 can be categorized in Type 2 (prominent neck, shoulder, and respiratory involvement but not ocular weakness) and Case 3 can be categorized in Type 1 (marked oculobulbar weakness with facial and tongue atrophy). EMG results varied in the three patients. However, RNS was normal in one patient and only mild

decrement was seen in another patient. SFEMG was positive in one patient and not tested in other two patients.

Treatment for classic MG patients consists of (1) symptomatic treatment such as acetylcholinesterase inhibitors, (2) chronic immunomodulatory treatment such as corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, cyclophosphamide, tacrolimus, and more recently rituximab, (3) rapid immunomodulatory treatment such as high dose steroid, TPE, or IVIG, and (4) surgical treatment such as thymectomy. MuSK MG patients tend to respond poorly to acetylcholinesterase inhibitors and may not respond as well to IVIG. The thymus gland is typically normal. Therefore, immunomodulatory treatments, both chronic and rapid, are more important for those with MuSK MG. All of our MuSK MG patients presented here also had poor response to pyridostigmine and have no evidence of a thymoma. With the exception of Case 1, who initially responded well to IVIG, all three cases were ultimately refractory to IVIG therapy.

Most MG patients respond well to steroid therapy. However, short- and long-term steroid use is associated with multiple and possibly severe side effects including susceptibility to infection (which can trigger a flare of symptoms in MG patients), diabetes, hypertension, gastrointestinal bleeding, mood swings, osteoporosis, and Cushingoid appearance. The patients' response to other immunosuppressive mediations varies depending on patient, and so do the side effects. Azathioprine can cause bone marrow suppression and liver dysfunction, cyclosporine can cause renal dysfunction and paresthesias, mycophenolate mofetil can cause gastrointestinal symptoms and susceptibility for infection, methotrexate and cyclophosphamide can also cause gastrointestinal symptoms, liver dysfunction, bone marrow suppression, and infection, tacrolimus can cause renal dysfunction and opportunistic infections [16]. Recently rituximab is reported to be beneficial for MuSK MG patients as a long-lasting treatment [17–19] and likely will become increasingly used to treat MuSK-MG. However, prolonged B-cell depletion is reported [20] in addition to minor side effects such as fever, nausea, headache, and dyspnea [16]. Angina, cardiac dysrhythmia, anemia, leukopenia, and thrombocytopenia also have been reported in MG patients [21]. Importantly; rituximab is currently not approved for treatment of MG and may not be covered by public and private insurers. The effect of IVIG also varies depending on individual.

Our study shows that maintenance TPE may be a viable alternative treatment for MuSK MG patients who fail to respond or are intolerant of standard immunosuppressive therapy. In the three cases reported here, we were able to achieve relatively prolonged periods of excellent symptom control using maintenance TPE. The frequency of treatment is adjusted based upon the patients' report of symptom control and the physicians' evaluation. Case 1 receives TPE every 4 weeks, but occasionally every 3 weeks when she has infection or predictable emotional or physical stress. She is stable with minimal symptoms without medications. Case 2 had frequent vascular access problems, and her symptoms remarkably worsened without TPE despite treatment with oral immune-modulating medications. Case 3 was also stable with modification of TPE frequency depending on her symptoms in conjunction with medications. She currently is not requiring TPE, but is receiving aggressive immunosuppression for HLH syndrome.

Our three patients did not experience any adverse events to TPE procedures such as hypotensive or allergic reactions, citrate side effects, bleeding episodes, and procedure-related anemia. The shortest interval of maintenance TPE employed with these patients is 7 days, which may be sufficient to recover from decreased coagulation factors, Hct, and immunoglobulin levels when liver and kidney functions are normal. However, the access for frequent TPE is always a concern and one patient had catheter-related infection twice. A fistula or a port placement may be required when peripheral access is poor. One of our patients has been able to receive maintenance TPE every 2–4 weeks for several years using only peripheral access, and another was treated with peripheral access exclusively. Infection has to be monitored carefully with periodical tests for WBC/neutrophil/lymphocyte counts and immunoglobulin levels since infectious risk is high in these patients due to immunosuppression.

CONCLUSIONS

We report three MuSK MG patients who have received maintenance TPE treatment with favorable outcome. Maintenance TPE may be an effective option for MuSK MG patients who cannot tolerate medications, or receive incomplete benefit from standard immunosuppression. The key to successful maintenance treatment at our institution has been to tailor the TPE frequency for each individual, and to modify the treatment interval in conjunction with medical management. In some patients, peripheral access may be adequate for even long-term TPE, but many patients will need alternative access. A fistula may be considered for such patients.

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