Long-term treatment of refractory myasthenia gravis with subcutaneous immunoglobulin

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Introduction

Myasthenia gravis (MG) is an autoimmune disease characterized by fatigue and weakness of skeletal muscles. Laryngeal myasthenia (when dysphonia is the initial and primary complaint) is a rare variant of MG (0.46%),[1] which may provide a diagnostic challenge. Although with adequate treatment majority of myasthenic patients can live productive lives with no or few symptoms, there is a distinct subset of patients who have a very difficult-to-control disease. Here we report two cases of treatment-refractory patients (one generalized and one initially isolated laryngeal MG) successfully managed by long-term application of subcutaneous immunoglobulin (SCIG).

Informed consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patients.

Case report no. 1

A 45-year-old woman was diagnosed with generalized myasthenia at the age of 17. Thymectomy was performed within 1 year and histology revealed hyperplastic thymus. Antibody against AChR was detected in her serum. Treatment with pyridostigmine, ephedrine, ambenonium-chloride, and methylprednisolone resulted only in temporal improvements. Chronic immunosuppression with cyclosporine (100 mg/day) has been tried in two periods for a total of 44 months, and azathioprine (100 mg/day) in three periods for a total of 91 months between 1988 and 2008. Yearly 2–3 plasma exchange (PLEX) or intravenous immunoglobulin (IVIG) therapies had to be applied during this period due to marked progressions. Since chronic immunosuppression did not result in complete remission, chronic steroid use (8–24 mg of methylprednisolone daily) could not be stopped for years and provoked osteoporotic vertebral compression fracture in 2006, as well as cataract and chronic central serous chorioretinopathy in 2013. As the yearly rate of marked relapses increased significantly, azathioprine (100 mg/day) has been re-introduced in 2012, but did not result in significant reduction in relapse rate within 3 years. IVIG and PLEX (4–6 times a year) were used several times during the past decade. IVIG provoked abdominal pain. A hydrothorax developed as a consequence of PLEX in 2013. In order to stabilize the symptoms of the patient as soon as possible, and to avoid these side effects and frequent hospitalization we started SCIG treatment in June, 2015 (Hizentra, 20 g/100 ml, CSL Behring, 8 g per week, 0.16 g/kg/week) with no adverse events or side effects.[2] Symptoms became stabile and then gradually improved upon SCIG treatment. After 3 months, we increased the dose to 10 g per week due to mild deterioration. Steroid use could be decreased gradually to 2 mg methylprednisolone per day. No extra steroid or PLEX was needed since the initiation of SCIG. The quantitative MG score for disease activity (QMG score)[3] was 19 before starting SCIG treatment and decreased onto 9 after 15 months. The myasthenia gravis quality of life (MG-QOL-R) [4] score was 27 before and improved to 18 after treatment for 15 months (Table 1). The concentration of AChR antibody did not change significantly (56.27 nmol/l before and 59.99 nmol/l 17 months after the initiation of SCIG).

Case report no. 2

A 47-year-old woman with primary antiphospholipid syndrome developed sudden onset dysphonia in June, 2010, with no detectable cause. She complained about generalized skeletal muscle weakness, muscle pain, and mild dysphagia in

Table 1. Patient characteristics before and after SCIG use.

Case No.	Age sex	Antibody status A = AChRA, M = MUSK	Thymus	Thym-ectomy	MG therapy before SCIG	Concurrent MG therapy	No. of PLEX/year prior to starting SCIG	No. of PLEX/ year after starting SCIG	MGFA score before SCIG	MGFA score after SCIG	MG-QOL-R score before SCIG	MG-QOL-R score after SCIG
1	45 F	A +	Hyperplasia	Yes	Mpred 8–24 mg/d, AZT 150 mg/d, Pyrido 300 mg/d	Mpred 2 mg/d, Pyrido 300 mg/d	5	0	19	9	27	18
2	47 F	A -, M -	No	No	Mpred 16–48 mg/d, Cy: 500 mg/month, Pyrido: 300 mg/d	Mpred 16 mg/d, MTX 15 mg/w, Pyrido: 300 mg/d	5	0	18	12	26	20

AChRA, acetylcholine receptor antibody; AZT, azathioprine; Cy, cyclophosphamide; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MG-QOL-R, myasthenia gravis quality of life; Mpred, methylprednisolone; MTX, methotrexate; MUSK, Muscle-specific kinase antibody; No., number; PLEX, plasma exchange; Pyrido, pyridostigmine; SCIG, subcutaneous immunoglobulin.

December, 2006. Brain computed tomography (CT) and magnetic resonance imaging (MRI), laboratory workup, chest CT, and repetitive nerve stimulation (RNS) of the axillary nerve were negative. Physical examination revealed pressure sensitive skeletal muscles, no dysphonia, dysphagia or muscle weakness. Electromyography (EMG) was characteristic for acute myositis. Histologic evaluation of the left deltoid muscle and muscle MRI showed negative result. She was categorized as having a 'possible myositis.' The patient was on azathioprine therapy (100 mg/day) only for 4 weeks because it caused intolerable nausea and abdominal pain. Hydroxychloroquine (6 months), then methylprednisolone and cyclosporine was started. In 2013 symptoms were worsening, mild weakness of the facial muscles and hip flexors, medium severity weakness of the neck flexors, mild dysphagia, mild atrophy of the tongue, and medium severity dysphonia was detected. RNS test of the axillary nerve was negative again, but the edrophonium-chloride test resulted in marked improvement, especially in her dysphonia. Laboratory tests for antibodies against AChR and muscle-specific kinase antibody (MUSK) were negative. Single-fiber EMG (SF-EMG) of the right extensor digitorum brevis muscle showed elevated mean consecutive difference (MCD) value (44.1 μs), and 55% of the potential pairs had increased jitter, suggesting mild impairment of neuromuscular transmission. In the right orbicularis oculi muscle a normal MCD value was found (27.3 μs), and <10% of the potential pairs had increased jitter. Initially isolated laryngeal MG was diagnosed and pyridostigmine was started which resulted in significant improvement. EMG showed a myogenic pattern 3 years before the diagnosis of MG in this patient. Besides to the co-occurrence of myositis and MG this may also be attributed to a noncharacteristic myopathic pattern as sometimes seen in myasthenic patients.[5,6] The patient's symptoms deteriorated markedly (bulbar signs and dyspnoea) and were treated with PLEX five times between July, 2013 and May, 2014. Since cyclosporine therapy (100 mg/day) for 17 months did not result in reduction of relapse rate it was changed to cyclophosphamide (3 times, monthly infusions of 800-500-500 mg). The fifth PLEX caused gravis anemia, alterations in hemostasis and a pre-shock stage of the patient. 20 g IVIG was added with good result two times within 2 weeks. In order to sustain the good condition of the patient, and to avoid the repeated exacerbations seen after PLEX and IVIG treatments, we started

SCIG treatment 1 week after applying the last IVIG therapy in July, 2014 (Hizentra, 20 g/100 ml, 6 g per week, 0.1 g/kg/week) with good effectivity and without any side effects.[2] After 6 months from initiation, the dose had to be elevated to 10 g, then, after another 11 months to 12 g (0.2 g/kg/week) due to mild deterioration. Steroid use could be decreased from an average of 28 mg to 16 mg methylprednisolone per day and had to be elevated two times temporally. QMG score was 18 before starting SCIG treatment and decreased onto 12 after 26 months. MGQOL-R score was 26 before and improved to 20 points after treatment for 26 months (Table 1).

Discussion

Treatment of acute exacerbations in MG with IVIG is well established.[7] The prevalence of treatment-refractory myasthenia is estimated to approximately 10% of patients with generalized disease.[8] Prevention of exacerbations by intermittent IVIG therapy in these patients has been demonstrated only in three studies. This treatment also provided a reduction of pyridostigmine, steroid and azathioprine.[2,9,10] In addition, SCIG offers the advantage of increased patient autonomy by home administration, lower rate of treatment-related reactions, and decrease of costs.

To date, only two reports are available about SCIG use in MG. Yoon and colleagues reported the long-term clinical follow up of one patient with AChR antibody-positive, generalized myasthenia.[11] In this case IVIG therapy has been switched to SCIG (12.8 g/week) with the possibility of dose reduction of 20%. Bourque and colleagues published a retrospective cohort study of chronic management of MG with SCIG in nine patients.[12] The average follow-up time was 6.8 months. All patients achieved a stable or improved Myasthenia Gravis Foundation of America (MGFA) classification, and there were statistically significant improvements in the myasthenia gravis-specific activities of daily living (MG-ADL) scale, MG-QOL and visual analog scales. In six patients the SCIG dose was significantly higher than the previous IVIG dose. Limited information is available about change in steroid requirement in these studies.

In this paper, we report successful stabilization of myasthenic symptoms of two therapy-refractory, unstable MG patients with SCIG. To our knowledge this is the first report of SCIG use in a patient with seronegative, initially isolated laryngeal myasthenia. Our patients remained stable by long-term SCIG treatment with lower doses of Ig compared with the patients in the literature. In both cases QMG score and MG-QOL-R scores improved significantly, the dose of steroid could be decreased. No significant progression or side effect of SCIG treatment occurred. Rituximab is an alternative option for therapy-refractory patients with milder clinical condition. Nonetheless, for long-term treatment one can consider introducing rituximab or mycophenolate mofetil in addition to SCIG in order to reduce the Ig needs of the patient.

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KD, MNV and JB conceived the study. EK collected the clinical data and prepared the first draft of the manuscript. KD, MNV, LCS and JB contributed to the preparation of the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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