Neuroendocrinology Letters Volume 41 No. 4 2020
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Comparison of quality of life and activity of daily living status of patients with myasthenia gravis treated with low-dose and high-dose prednisolone

Masaaki Katsuki[1], Hirotaka Sugahara[2], Yuka Kojima[2], Kanae Yamashita[2], Hiroshi Moriuchi[1], Toshio Kubota[1], Masayuki Masuda[3], Mitsuru Irikura[2]

1 Center of Pharmaceutical Care for Community Health, Daiichi University of Pharmacy, Fukuoka, Japan
2 Laboratory of Evidence-Based Pharmacotherapy, Daiichi University of Pharmacy, Fukuoka, Japan
3 Department of Neurology, Tokyo Medical University, Tokyo, Japan

Correspondence to: Masaaki Katsuki, Ph.D
Center of Pharmaceutical Care for Community Health, Daiichi University of Pharmacy, Fukuoka, Japan
TEL.: +81-92-541-0161; FAX: +81-92-553-5698;
E-MAIL: m-katsuki@daiichi-cps.ac.jp

Submitted: 2020-05-26 Accepted: 2020-09-10 Published online: 2020-09-20

Key words: **Myasthenia gravis; prednisolone; quality of life; activity of daily living; questionnaire; minimal manifestation**

Neuroendocrinol Lett 2020; **41**(4):173–178 **PMID:** 33307652 NEL410420A03

Abstract

OBJECTIVES: To compare the effect of low-dose prednisolone (PSL) (≤5 mg/day) and high-dose PSL (>5 mg/day) therapy on the QOL and activity of daily living (ADL) in patients with MG.
METHODS: A total of 679 patients with MG underwent a survey using Japanese versions of the MG-QOL 15-J and MG-ADL scales. Higher scores of these scales suggest deterioration of the QOL and ADL, respectively.
RESULTS: The total MG-QOL 15-J scores of the high-dose group (27.0±13.8) were significantly higher than those of the low-dose group (20.9±14.6). Similarly, the total MG-ADL scores of the high-dose group (6.3±4.1) were significantly higher than those of the low-dose group (5.3±4.1).
CONCLUSION: These results showed that the QOL of patients in the low-dose group appeared better than that in the high-dose group. Low-dose PSL therapy may help achieve minimal manifestations level in Japanese patients with MG.

Abbreviations:

ADL	- Activity of daily living
MG	- Myasthenia gravis
MM	- Minimal manifestations
PSL	- prednisolone
QOL	- Quality of life

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune inflammatory disease of the neuromuscular junction which is characterized by muscle weakness and fatigability. The condition is typically caused by autoantibodies against muscle nicotinic acetylcholine receptors (Meriggioli & Sanders, 2009). The clinical hallmark of the disease is fluctuating muscle weakness that worsens with exertion. Ocular muscle weakness is the most common presenting symptom that usually results in asymmetric ptosis and diplopia. The symptoms often extend to bulbar, limb, axial, and respiratory muscles, resulting in generalized MG. In a minority of patients, the symptoms are limited to the ocular muscles (i.e., ocular MG) (Gilhus, 2016, Nair *et al.* 2014). Treatment strategies for

MG include: (1) improving neuromuscular transmission with the use of acetylcholinesterase inhibitors; (2) treatment of acute exacerbations (e.g., plasma exchange, intravenous immunoglobulin therapy); (3) immunosuppressive therapy; and (4) thymectomy (Sieb, 2014). Nonetheless, many patients with MG experience insufficient improvement in addition to long-term side effects of oral corticosteroids (Gilhus, 2009, Sanders & Evoli, 2010, Masuda *et al.* 2012, Utsugisawa *et al.* 2014).

Corticosteroids have been widely used for the treatment of MG either as the sole therapy or in combination with thymectomy (Pascuzzi *et al.* 1984, Suzuki *et al.* 2011). However, the side effects of corticosteroids may adversely affect the quality of life (QOL) of patients. In addition, there are few randomized controlled trials of steroid therapy for MG, and the optimal dose and dosing method have not been established.

Disease severity and the dose of oral corticosteroids are major factors that negatively affect the self-perceived QOL of patients with MG (Masuda *et al.* 2012, Utsugisawa *et al.* 2014). Therefore, reducing both the severity of the illness and the dose of oral corticosteroids are key imperatives (Masuda *et al.* 2012, Utsugisawa *et al.* 2014). Several studies have compared the relationship of the QOL and clinical parameters of MG with the associated treatment; these studies suggest that it is feasible to achieve minimal manifestations (MM) (or better) status using prednisolone (PSL) doses of ≤5 mg/day (MM5) (Masuda *et al.* 2012, Utsugisawa *et al.* 2014, Jaretzki, 2000). Achieving an early return to such a state may enable patients to lead a normal lifestyle without worrying about the adverse effects of corticosteroids (Utsugisawa *et al.* 2014). The Japanese clinical guidelines (GLs) for MG were published in 2014 (Murai, 2015). The GLs also recommend postintervention status of MM5 as the therapeutic target (according to the MG Foundation of America Classification) (Jaretzki, 2000).

However, there is no robust evidence to support the treatment with PSL at doses of ≤5 mg/day in Japan. Therefore, the primary objective of this study was to identify the better treatment strategy for patients with MG between the low-dose (≤5 mg/day) and high-dose PSL (>5 mg/day) therapy. The secondary objective was to assess whether low-dose PSL therapy can help achieve minimal manifestations status in patients with MG. We examined these outcomes in terms of symptoms and adverse effects that affect the QOL and/or activity of daily living (ADL).

METHODS

MG patients

We conducted a survey in collaboration with the Japan Myasthenia Gravis Association (Kyoto). Questionnaires were mailed to 1307 members of the association. Of these, 679 members responded to the survey. This survey was conducted after obtaining informed consent in writing from the respondents. The study was approved by the Ethics Committee of the Daiichi University of Pharmacy.

Japanese version of the MG-QOL 15-J

In this study, we used the Japanese version of the MG-QOL 15-J (Masuda *et al.* 2012, Burns *et al.* 2008), which comprises of the following 15 items: 1) "I am frustrated by my condition"; 2) "I have trouble using my eyes"; 3) "I have trouble eating"; 4) "I have limited my social activity because of my condition"; 5) "My condition limits my ability to enjoy hobbies and fun activities"; 6) "I have trouble meeting the needs of my family"; 7) "I have to make plans around my condition"; 8) "My occupational skills and job status have been negatively affected"; 9) "I have difficulty speaking"; 10) "I have trouble driving"; 11) "I am depressed about my condition"; 12) "I have trouble walking"; 13) "I have trouble getting around as my peers do (for example, in public places)"; 14) "I feel overwhelmed by my condition"; and 15) "I have trouble performing my personal grooming needs."

Each item was evaluated using a 5-point Likert scale (disagree, tend to agree, agree a little, agree, and agree very strongly). The maximum possible score is 60 points. The higher the score, the lower is the quality of life of the patient because of intensification of MG.

MG-ADL questionnaire

MG-ADL questionnaire assesses the following 8 parameters: 1) "speaking"; 2) "chewing"; 3) "swallowing"; 4) "breathing"; 5) "ability to brush teeth or comb hair"; 6) "ability to rise from a chair"; 7) "double vision"; 8) "eyelid droop". Each parameter is scored on a scale ranging from 0 (normal) to 3 (most severe) points. The maximum possible score is 24 points. The higher the score, the greater are the limitations of the patient in ADL caused by intensification of MG (Wolfe *et al.* 1999, Muppidi *et al.* 2011).

Definition of minimal manifestations (MM) status and study groups

In this study, we defined MM as "the state wherein minimal muscle weakness exists, but there is no problem in performing the ADL". The MM state cannot be assessed based only on the questionnaire; therefore, we defined the MM state as follows: MG-ADL scale score 0–8 and patient can perform daily activities. In addition, we divided patients into two groups, i.e., low-dose group (PSL≤5mg/day) and high-dose group (PSL>5mg/day).

RESULTS

Characteristics of the patients in the low-dose and high-dose groups

The characteristics of the study population are summarized in Table 1. There was no significant difference between the low-dose and high-dose groups with

Tab. 1. Characteristics of MG patients in the low-dose and high-dose groups

	Total (n=679)	Low-dose group (≤5 mg/day) (n=219)	High-dose group (> 5 mg/day) (n=194)	*P* value
Characteristics				
Current age (years)	59.4±16	59.0±16	56.6±16.4	0.0797
Age of onset (years)	41.1±16	42.9±17	39.3±18.6	0.0357*
Percentage of women	70.8% (n=481)	74.9% (n=164)	72.9% (n=139)	0.5935
Method of therapy				
Duration of PSL therapy (years)	9.0±10.2	11.7±9.72	12.5±11.3	0.7624
Immunosuppressive drugs	48.0% (n=326)	52.1% (n=114)	66.0% (n=128)	0.0049*
Cholinesterase inhibitors	56.3% (n=382)	62.1% (n=130)	66.0% (n=116)	0.9198
Other drugs	24.7% (n=168)	32.0% (n=76)	29.9% (n=58)	0.6699
Steroid pulse	31.4% (n=379)	33.8% (n=127)	42.8% (n=94)	0.0596
Powerful treatment	23.4% (n=159)	25.1% (n=55)	32.5% (n=64)	0.0786
MG state				
During the most severe, there is trouble in the food and drink, etc.	66.1% (n=449)	65.8% (n=144)	78.4% (n=152)	0.0043*
Status of Thymus				
Thymoma	23.7% (n=161)	22.8% (n=50)	26.8% (n=52)	0.3626
Thymectomy	65.8% (n=447)	66.7% (n=146)	73.7% (n=143)	0.1584
Side effects				
Cushing-like appearance	56.8% (n=386)	66.7% (n=146)	75.8% (n=147)	0.0505
Hirsutism	23.0% (n=156)	27.4% (n=60)	32.0% (n=62)	0.3318
Weight gain	33.4% (n=227)	38.8% (n=85)	42.3% (n=82)	0.4837
Gastrointestinal disorder	24.6% (n=167)	30.1% (n=66)	32.5% (n=63)	0.6706
Eyesight deterioration	34.3% (n=233)	39.7% (n=87)	46.4% (n=90)	0.1954
Diabetes	15.6% (n=106)	15.1% (n=33)	22.2% (n=43)	0.0574
Bone fracture	16.9% (n=115)	21.4% (n=47)	23.1% (n=44)	0.7227
Back pain	35.3% (n=240)	43.8% (n=96)	11.3% (n=22)	0.8429
Glaucoma	8.1% (n=55)	10.0% (n=22)	11.3% (n=22)	0.7499
Cataract	29.6% (n=201)	33.3% (n=73)	37.6% (n=73)	0.4095
Antibody status				
Anti-acetylcholine receptor antibody positivity	59.8% (n=406)	65.3% (n=143)	64.4% (n=125)	0.666
Anti-musk antibody positivity	3.1% (n=21)	1.8% (n=4)	6.7% (n=13)	0.0228*
Anti-Lrp4 antibody positivity	0.1% (n=1)	0.5% (n=5)	0% (n=0)	1
Seronegative	10.5% (n=71)	13.1% (n=28)	11.3% (n=22)	0.6509

*p<0.05, PSL, prednisolone

respect to most variables. However, significant between-group differences were observed with respect to the "age of onset", "immunosuppressive drugs for therapy", response to the item "during the most severe period, there is trouble in eating food and drinking, *etc.*", and "anti-musk antibody positivity".

Correlations between clinical factors and QOL

We investigated the clinical factors that had an influence on the QOL based on the 12 items in the questionnaire. The "MG-ADL scale score" showed the greatest influence on the QOL (*t* value=17.49) (Table 2). The other items associated with *t* values ≥2 were "current PSL dose" (*t* value=3.66), "at the time of the most severe period, there is trouble in eating food and drinking, *etc.*" (*t* value=3.10), and "side effects" (*t* value=2.46) (Table 2).

Correlation of MG symptoms and QOL

We examined the influence of the MG symptoms on the QOL. The symptoms are the eight items in the MG-ADL scale. The item that showed the greatest influence on the QOL was the "ability to rise from a chair" (*t* value=7.88) (Table 3). In order of intensity of influence, the other items were "breathing" (*t* value=4.52),

Tab. 2. Correlation of clinical factors and the QOL of MG patients

Clinical factor	*t* value
MG-ADL scale score	17.49
Current dose of PSL	3.66
At the time of the most severe, there is trouble in food and drink, etc.	3.10
Side effects of PSL	2.46
Age of onset	1.97
Age	1.62
Maximum dose taken in the past	1.02
Treatment	0.51
Sex	0.28
Total dose period	0.19
Thymoma	0.17
1 year ago dose	0.01

MG, myasthenia gravis; QOL, quality of life; ADL, activity of daily living; PSL, prednisolone

"eyelid droop" (*t* value=4.50), "chew" (*t* value=3.94), "talking" (*t* value=3.29), "ability to brush teeth or comb hair" (*t* value=3.06), and "double vision" (*t* value=2.99) (Table 3).

Tab. 3. Correlations of MG symptoms and QOL of MG patients

Symptoms of MG	*t* value
Ability to rise from a chair	7.88
Breathing	4.52
Eyelid droop	4.50
Chew	3.94
Talking	3.29
Ability to brush teeth or comb hair	3.06
Double vision	2.99
Swallowing	1.74

MG, myasthenia gravis; QOL, quality of life

Correlation between side effects of PSL and the QOL

Table 4 presents the correlation between the side effects of PSL and the QOL of MG patients. "Gastrointestinal disorder" (*t* value=4.93) had the greatest effect on the QOL. The other side effects that influenced the QOL were "eyesight deterioration" (*t* value=3.29), "backache" (*t* value=2.82), and "weight gain" (*t* value=2.14) (Table 4).

Tab. 4. Correlation of the side effects of PSL and QOL of MG patients

Side effects	*t* value
Gastrointestinal disorder	4.93
Eyesight deterioration	3.29
Backache	2.82
Weight gain	2.14
Diabetes mellitus	1.82
Cataract	1.14
Fracture	0.83
Hirsutism	0.79
Glaucoma	0.74
Cushing-like appearance	0.40

PSL, prednisolone; QOL, quality of life; MG, myasthenia gravis

Total scores of MG-QOL 15-J and the number of MG patients who achieved MM status in the low-dose and high-dose groups

The total MG-QOL 15-J scores were calculated by summing the numeric scores for the 15 items. The total MG-QOL 15-J score of the high-dose group (27.0±13.8) was significantly greater than that of the low-dose group (20.9±14.6) (Table 5). Similarly, the number of MG patients who achieved MM in the low-dose group (n=94) was significantly greater than that in the high-dose group (n=49)

The 8 parameters and total scores of MG-ADL in the low-dose and high-dose groups

Each parameter is scored on a scale ranging from 0 (normal) to 3 (most severe) points. The total MG-ADL scores were calculated by summing the numeric scores for the 8 parameters. As a result, significant between-group difference was observed with respect to the "Breathing". In addition, the total MG-ADL score of the high-dose group (6.3±4.1) was significantly greater than that of the low-dose group (5.3±4.1) (Table 6).

Correlation of QOL by ADL

Since the QOL is affected by the patient's ADL, we normalized the QOL values by ADL values. To obtain more reliable values of the QOL, we calculated the QOL/ADL ratio for the low- and high-dose groups (Fig. 1). The value of the high-dose group (6.2) was significantly greater than that of the low-dose group (4.8).

DISCUSSION

In this study, we used MG-QOL 15-J and MG-ADL to compare the QOL of patients treated with low-dose and high-dose PSL. There were significant between-group differences with respect to the age of onset, immunosuppressive drugs for therapy, and anti-musk antibody positivity between the low- and high-dose groups. Patients with MG are commonly classified into two subgroups according to the age of onset: early onset MG (EOMG) and late onset MG (LOMG) (Aarli, 1999). Patients in the LOMG subgroup typically show good response to PSL therapy; therefore, it is relatively easy for these patients to achieve MM level with PSL dose of ≤5 mg per day (Nagane *et al.* 2011). The age of onset of MG in the high-dose group (39.3±18.6 years) was lower than that in the low-dose group (42.9±17 years). The percentage of patients who received concomitant treatment with immunosuppressive drugs in the high-dose group (66.0%) was higher than that in the low-dose group (52.1%). In general, use of immunosuppressive drugs in MG patients is recommended after thymectomy (when the effect of PSL is insufficient) or in case of development of side effects of corticosteroids. High

Tab. 5. Total scores of MG-QOL 15-J and the number of MG patients who achieved MM status in the low-dose and high-dose groups

	Low-dose group *n*=219	High-dose group *n*=194	*P* value
MG-QOL 15-J	20.9±14.6	27.0±13.8	0.0001*
Number of MG patients who achieved MM	94 (42.9%)	49 (25.3%)	0.0002*

*p<0.05, MG, myasthenia gravis, MG-QOL, myasthenia gravis-quality of life; MM, minimal manifestations

Tab. 6. The 8 parameters and total scores of MG-ADL in the low-dose and high-dose groups

	Low-dose group *n*=219	High-dose group *n*=194	*P* value
1. Speaking	0.55±0.78	0.61±0.81	0.45
2. Chewing	0.47±0.58	0.56±0.57	0.1292
3. Swallowing	0.60±0.60	0.67 ±0.61	0.2726
4. Breathing	0.48±0.56	0.63±0.61	0.0274*
5. Ability to brush teeth or comb hair	0.51 ±0.75	0.59 ±0.73	0.2183
6. Ability to rise from a chair	0.69±0.76	0.78±0.81	0.3296
7. Double vision	1.10±1.11	1.23±1.15	0.2608
8. Eyelid droop	1.11±1.03	1.22 ± 1.06	0.2926
Total MG-ADL scores	5.3±4.1	6.3±4.1	0.0342*

*p<0.05, MG-ADL, myasthenia gravis-activity of daily living

dose of PSL is typically used due to worsening of MG symptoms; this likely explains the greater frequency of use of immunosuppressive drugs in the high-dose group. Recently, an early aggressive treatment strategy for MG has been proposed; this strategy entails the use of low-dose PSL in conjunction with immunosuppressive drugs at an early stage, which facilitates rapid resolution of MG symptoms in a short period (Nagane *et al.* 2011). Therefore, we suggest that use of immunosuppressive drugs may offer benefit in the low-dose group.

We investigated the correlates of the QOL of patients with MG. We found that the MG-ADL scale was the most important correlate of QOL. In addition, we also observed the important effect of current dose and the side effects of PSL on the QOL. Availability of therapy of steroid (PSL) for MG patients was noticed in many studies (Gilhus, 2009, Grob *et al.* 2008, Kobayashi *et al.* 2006, Luchanok & Kaminski., 2008, Elrod & Weinberg, 2004). Among the MG symptoms, the ability to rise from a chair showed the greatest impact on the QOL. Since muscle weakness and fatigue are typical symptoms of MG (Gilhus, 2016), it is conceivable that the t values of these factors would tend to be high. Finally, the gastrointestinal side-effects of PSL had the highest t value. Diabetes mellitus, fractures (osteoporosis), and eyesight deterioration are some of the common side effects of PSL; however, gastrointestinal side-effects are readily perceived by the patient and hence the higher rating.

Percentage of the item "during the most severe period, there is trouble in eating foods and drinking etc." in the high-dose group (78.4%) was higher than

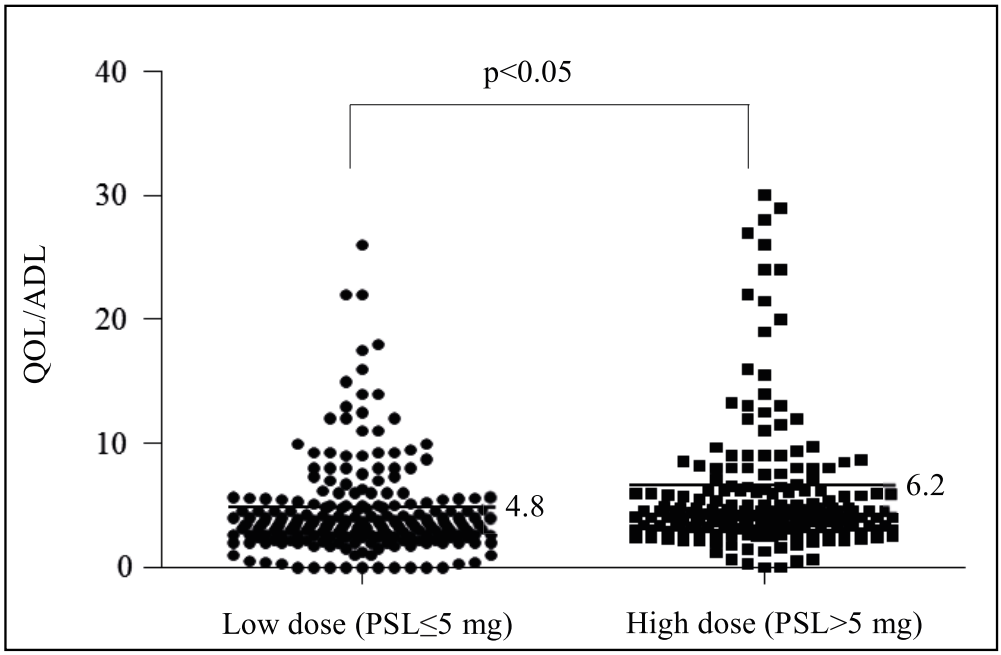

Fig. 1. Correlation between QOL and ADL in the low-dose and high-dose groups PSL, prednisolone; QOL, quality of life; ADL, activity of daily living

that in the low-dose group (65.8%). Similarly, both the total MG-QOL 15-J scores and total MG-ADL scores were significantly higher in the high-dose group than those in the low-dose group. These results suggested that the side effects of PSL could be controlled by lowering the dose of PSL, and possible concomitant use of immunosuppressive drugs. The rate of achievement of MM state in the low-dose group (42.9%) was higher than that in the high-dose group (24.7%). In this study, we have used subjective MG-ADL questionnaire as an evaluation method of the MG state. However, there was limitation in this study. The MG Foundation of America (MGFA) classification is widely used as an evaluation method of the MG state by physicians and would be more convenient as the definition of the MM status (Jaretzki *et al.* 2000). On the other hand, MG-ADL questionnaire is the evaluation method that patient mention is subjective. Therefore, further experiments would be required to evaluate by using the MGFA classification with the low-dose and high-dose prednisolone in the future.

There results may suggest that low-dose PSL therapy, possibly with concomitant use of immunosuppressive agent, can help improve the QOL and maintain the MM status.

STATISTICS

Statistical analyses were performed using GraphPad Prism, version 3.00 (GraphPad, Inc., La Jolla, CA, USA). Data are presented as mean±standard deviation. Low-dose group and high-dose group were compared using Mann–Whitney U-test for continuous variables (e.g., age, duration of PSL therapy) and Fisher's exact test for categorical variables (e.g., sex, incidence rates of side effects). P values <0.05 were considered indicative of statistical significance. Correlates of QOL were identified using multiple regression analysis using Ekuseru-Toukei 2015 (Social Survey Research Information Co., Ltd., Tokyo, Japan); t values ≥ 2.0 were considered statistically significant.

ACKNOWLEDGMENTS

We are deeply grateful to the Japan Myasthenia Gravis Association (Kyoto) for supporting this research and for generously sharing their experiences with us.

REFERENCES

1 Aarli JA., 1999 Late-onset myasthenia gravis: a changing scene. Arch Neurol. **56**: 25–27.
2 Burns TM., Conaway MR., Cutter GR., Sanders DB., 2008 Muscle Study Group. Less is more, or almost as much: A 15-item quality-of-life instrument for myasthenia gravis. Muscle Nerve. **38**: 957–963.
3 Elrod RD., Weinberg DA., 2004 Ocular myasthenia gravis. Ophthalmol Clin North Am. **17**: 275–309.
4 Gilhus NE., 2009. Autoimmune myasthenia gravis. Expert Rev Neurother. **9**: 351–358.
5 Gilhus NE., 2016. Myasthenia Gravis. N Engl J Med. **29**: 2570–2581.
6 Grob D., Brunner N., Namba T., Pagala M., 2008 Lifetime course of myasthenia gravis. Muscle Nerve. **37**: 141–149.
7 Jaretzki A 3rd., Barohn RJ., Ernstoff RM., Kaminski HJ., Keesey JC., Penn AS., Sanders., DB., 2000 Myasthenia gravis: recommendations for clinical research standers. Task Force of the Medical Scientific Advisory Board of Myasthenia Gravis Foundation of America. Neurology. **55**: 16–23.
8 Jaretzki A 3rd., Barohn RJ., Ernstoff RM., Kaminski HJ., Keesey JC., Penn AS., Sanders DB., 2000 Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Ann Thorac Surg. **70**: 327–34.
9 Kobayashi Y., Fujii Y., Yano M., Sasaki H., Yukiue H., Haneda H., Suzuki E., Endo K., Kawano O., 2006 Preoperative steroid pulse therapy for invasive thymoma: clinical experience and mechanism of action. Cancer. **106**: 1901–1907.
10 Luchanok U., Kaminski HJ., 2008 Ocular myasthenia: diagnostic and treatment recommendations and the evidence base. Curr Opin Neurol. **21**: 8–15.
11 Masuda M., Utsugisawa K., Suzuki S., Nagane Y., Kabasawa C., Suzuki Y., Utsumi H., Fujihara K., Uchiyama S., Suzuki N., 2012 The MG-QOL15 Japanese version: validation and associations with clinical factors. Muscle Nerve. **46**: 166–173.
12 Meriggioli MN., Sanders DB., 2009. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol. **8**: 475–490.
13 Muppidi S., Wolfe GI., Conaway M., Burns TM., 2011 MG Composite and MG-QOL15 Study Group. MG-ADL: still a relevant outcome measure. Muscle Nerve. **44**: 727–731.
14 Murai H., 2015 Japanese clinical guidelines for myasthenia gravis: putting into practice. Clin Exp Neuroimmunol. **6**: 21–31.
15 Nagane Y., Suzuki S., Suzuki N., Utsugisawa K., 2011 Early aggressive treatment strategy against myasthenia gravis. Eur Neurol. **65**: 16–22.
16 Nair AG., Patil-Chhablani P., Venkatramani DV., Gandhi RA., 2014. Ocular myasthenia gravis: A review. Indian J Ophthalmol. **62**: 985–991.
17 Pascuzzi RM., Coslett HB., Johns TR., 1984 Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. Ann Neurol. **15**: 291–298.
18 Sanders DB., Evoli A., 2010. Immunosuppressive therapies in myasthenia gravis. Autoimmunity. **43**: 428–435.
19 Sieb JP., 2014. Myasthenia gravis: an update for the clinician. Clin Exp Immunol. **175**: 408–418.
20 Suzuki Y., Utsugisawa K., Suzuki S., Nagane Y., Masuda M., Kabasawa C., imizu Y., Utsumi H., Uchiyama S., Fujihara K., Suzuki N., 2011 Factors sociated with depressive state in patients with myasthenia gravis: A multicenter ross-sectional study. BMJ Open 1, e000313.
21 Utsugisawa K., Suzuki S., Nagane Y., Masuda M., Murai H., Imai T., Tsuda E., Konno S., Nakane S., Suzuki Y., Fujihara K., Suzuki N., 2014et Health-related quality of life and treatment targets in myasthenia gravis. Muscle Nerve. **50**: 493–500.
22 Wolfe GI., Herbelin L., Nations SP., Foster B., Bryan WW., Barohn RJ., 1999 Myasthenia gravis activities of daily living profile. Neurology. **52**: 1487–1489.