RESEARCH PAPER

Oral corticosteroid dosing regimen and long-term prognosis in generalised myasthenia gravis: a multicentre cross-sectional study in Japan

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ABSTRACT

Objective We examined the correlation between the dosing regimen of oral prednisolone (PSL) and the achievement of minimal manifestation status or better on PSL ≤5 mg/day lasting >6 months (the treatment target) in patients with generalised myasthenia gravis (MG).

Methods We classified 590 patients with generalised MG into high-dose (n=237), intermediate-dose (n=187) and low-dose (n=166) groups based on the oral PSL dosing regimen, and compared the clinical characteristics, previous treatments other than PSL and prognosis between three groups. The effect of oral PSL dosing regimen on the achievement of the treatment target was followed for 3 years of treatment.

Results To achieve the treatment target, ORs for low-dose versus high-dose regimen were 10.4 (P<0.0001) after 1 year of treatment, 2.75 (P=0.007) after 2 years and 1.86 (P=0.15) after 3 years; and those for low-dose versus intermediate-dose regimen were 13.4 (P<0.0001) after 1 year, 3.99 (P=0.0003) after 2 years and 4.92 (P=0.0004) after 3 years. Early combined use of fast-acting treatment (OR: 2.19 after 2 years, P=0.02; OR: 2.11 after 3 years, P=0.04) or calcineurin inhibitors (OR: 2.09 after 2 years, P=0.03; OR: 2.36 after 3 years, P=0.02) was associated positively with achievement of treatment target.

Conclusion A low-dose PSL regimen with early combination of other treatment options may ensure earlier achievement of the treatment target in generalised MG.

INTRODUCTION

Long-term full remission without treatment is uncommon in myasthenia gravis (MG).[1–5] Only <10% of patients with MG achieve Myasthenia Gravis Foundation of America (MGFA) postintervention status of complete stable remission (CSR).[4–7] Therefore, treatment strategies should consider the probability of prolonged treatment, and aim for maintaining health-related quality of life (QOL) and mental health.[8] The recent international consensus guidance for management of MG proposes minimal manifestation (MM) status or better as a goal for the treatment of MG.[9] Our research group has also proposed that MM status or better with prednisolone (PSL) 5 mg/day or lower (MM-or-better-5mg)

may be a more practical treatment goal than CSR and achievable by more patients, and that this goal yields patient satisfaction essentially equivalent to CSR based on patients' QOL.[5]

Among the various immunosuppressive therapies, oral corticosteroids remain the most common agent used for long-term immunosuppression in the management of MG.[10] In traditional therapy, oral corticosteroids have been used at high doses in an escalation and de-escalation fashion. However, there are no reported data supporting the claim that treatment with high-dose oral steroids increases the rate of complete remission in MG, and epidemiological research shows no change in complete remission rate before and after use of oral steroids became widespread.[2] Many patients continue to have impaired QOL because of insufficient improvement and long-term steroid-related adverse effects.[1 11] Furthermore, our previous survey showed that higher PSL dose and longer PSL treatment do not ensure better outcome.[12] Even in the international consensus guidance, there is no internationally accepted standard dosing regimen for oral corticosteroids.[9]

We conducted a multicentre cross-sectional study to examine the correlation between the dosing regimen of oral PSL and the achievement of practical treatment goal. Patients with MG were classified based on the dosing regimen of oral PSL during the whole course of treatment into three groups: high-dose, intermediate-dose and low-dose groups. We examined the effect of oral PSL dosing regimen on the achievement of favourable status during 3 years of treatment in a large population of patients with MG.

METHODS
Data collection

The study was conducted by the Japan MG Registry (JAMG-R) participated by 13 neurological centres (JAMG-R Group) in Japan. To avoid potential bias, we studied consecutive patients over a short period of 4 months in this multicentre study. We identified 1088 patients with various stages of MG who attended the hospitals between April and July 2015. Among these patients, 638 patients with generalised MG were evaluated. Since we classified

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Table 1 Differences in characteristics of present status in patients classified by oral PSL dosing regimen

	High-dose group (n=237)	Intermediate-dose group (n=187)	Low-dose group (n=166)	P value
Demographics				
Gender (% women)	63.3	68.6	71.9	0.32
Age (years), range	57.1±15.4 (18–88)	56.4±16.0 (16–90)	59.6±16.7 (19–91)	0.16
Age of onset (years), range	42.3±16.8 (0.9–76)*	46.4±16.9 (1–77)*	51.1±19.4 (0–89)*	<0.0001*
Disease duration (years), range	15.0±10.0 (1–60)*	10.1±8.9 (0.1–47.4)	8.9±9.1 (0.3–55)	<0.0001*
Antibody status				
AChRAb-positive (%)	88.7	86.2	76.0†	0.002†
MuSKAb-positive (%)	3.8	2.7	3.0	0.35
Thymus status				
Thymectomy (%)	83.1†	65.8†	36.1†	<0.0001†
Thymoma (%)	29.1†	38.5†	22.9†	0.006†
Postintervention status				
MM or better (%)	52.9	50.3	56.7	NS
I or worse (%)	47.0	49.8	41.4	NS
Current treatment				
Daily dose of PSL (mg), range	4.5±5.1 (0–40)	7.1±5.8 (0–30)*	4.8±3.2 (0–15)	<0.0001*
Combination of CNIs (%)	65.1	69.6	65.9	0.59
Daily dose of tacrolimus (mg), range	1.8±1.4 (0–5)	2.1±1.2 (0–4)	2.2±1.1 (0–3)	0.09
Daily dose of pyridostigmine (mg), range	58.2±79.4 (0–360)*	80.7±77.7 (0–240)*	72.5±77.1 (0–240)*	0.003*

*Significant difference detected by one-way ANOVA followed by the Tukey-Kramer test.
†Pearson's X^2 test.
AChRAb, acetylcholine receptor antibody; ANOVA, analysis of variance; CNIs, calcineurin inhibitors; I, improved; MM, minimal manifestations; MuSKAb, muscle-specific kinase antibody; NS, not significant; PSL, prednisolone.

patients by PSL dose regimen at the time of treatment initiation, we excluded 48 patients whose PSL dosing regimens appeared not to be decided at the beginning of treatment or were changed during the course of treatment. Finally, 590 patients with MG were analysed. All these patients provided written informed consent to be subject in the present study.

Diagnosis of MG was based on clinical findings (fluctuating symptoms with easy fatigability and recovery after rest) with amelioration of symptoms after intravenous administration of anticholinesterase, decremental muscle response to a train of low-frequency repetitive nerve stimuli, or the presence of antibodies against skeletal muscle acetylcholine receptor (AChRAb) or muscle-specific tyrosine kinase (MuSKAb). Serum AChRAb levels were determined by a radioimmunoassay using ^{125}I-α-bungarotoxin, and levels ≥0.5 nM were regarded as positive. Serum MuSKAb levels were measured using a commercially available radioimmunoprecipitation assay (Cardiff, UK). Single-fibre electromyography[13] was not performed routinely.

The following basic data of patients with MG were collected: gender, age, age at onset, disease duration, MGFA classification,[6] quantitative MG (QMG) score,[6] and AChRAb and MuSKAb status. Treatment-related data were also extracted, including MGFA postintervention status,[6] history of thymectomy, thymic histology, current PSL dose, peak PSL dose, PSL dosing regimen, total dose of high-dose intravenous methylprednisolone (HMP), use of calcineurin inhibitors (CNIs), use of pyridostigmine, plasma exchange/plasmapheresis (PE/PP), intravenous immunoglobulin (Ig) and early fast-acting treatment (EFT).[14] EFT was defined as the treatment strategy that attempted to achieve MM status early using fast-acting therapy such as PE/PP alone, PE/PP combined with HMP, HMP alone or intravenous Ig starting within 6 months of treatment initiation, and maintain the improved clinical status with the lowest possible dose of oral PSL.[15] We did not analyse other oral immunosuppressants such as azathioprine and mycophenolate mofetil, because use of these agents for MG is currently not covered by

the Japanese health insurance system. The PSL dosing regimens for the whole course of treatment were classified into three categories: high-dose regimen with an escalation and de-escalation schedule, intermediate-dose regimen and low-dose regimen. We set a maximum dose of oral PSL for each dosing regimen. In the high-dose group, PSL was given following an escalation schedule until symptoms improved sufficiently or until a maximum dose of 50–60 mg/day was reached. In the low-dose group, PSL was maintained at a maximum dose of 20 mg/day (usually ≤10 mg/day). When the symptoms did not improve sufficiently even when the dose was titrated up to 20 mg/day, other treatment options such as CNIs and EFT (PE/PP, intravenous Ig or HMP) were added to improve residual symptoms rapidly. The intermediate-dose group included patients who were treated with PSL ≥20 mg/day for longer than 3 months or who did not belong to either the high-dose or low-dose group. In all patients, the PSL dosing regimen was decided at the time of treatment initiation and was not changed during the course of treatment.

All clinical information and blood samples were collected after informed consent was obtained from each subject.

Statistical analysis

The clinical, immunological and therapeutic parameters were compared between three groups using one-way analysis of variance (ANOVA) followed by Tukey-Kramer test for continuous variables or Pearson's X^2 test for categorical variables. Also, multivariate logistic regression modelling was performed to determine independent predictive factors for MM-or-better-5mg at 1, 2 and 3 years after treatment was started. Factors entered into the model included clinical severity at the time of study; antibody status; thymectomy; treatment with CNIs, intravenous Ig, PE/PP, and EFT; and dosing regimen of oral PSL (high-dose, intermediate-dose and low-dose regimen). All continuous data are expressed as mean±SD. A probability <0.05 was considered

Table 2 Comparisons of maximum severity, achievement of MM-or-better-5mg for ≥6 months and other treatments in patients classified by oral PSL dosing regimen

	High-dose group (n=237)	Intermediate-dose group (n=187)	Low-dose group (n=166)	P value
Maximum severity through the entire course				
MGFA clinical classification (%)(II/III/IV/V)	37.8/27.7/12.2/22.3*	51.9/35.3/3.7/9.1	72.4/22.2/0.6/4.8	<0.0001*
Worst QMG score (range)	18.6±7.9 (3–39)†	14.4±6.4 (1–39)	13.9±6.3 (4–39)	<0.0001†
Achievement of MM-or-better-5mg for ≥6 months				
After 1 year of treatment (%)	9.6	11.4	52.1*	<0.0001*
After 2 years of treatment (%)	29.9	30.8	61.2*	<0.0001*
After 3 years of treatment (%)	44.1	36.4	64.1*	<0.0001*
Previous treatments other than PSL				
Accumulated dose of HMP (g), range	12.9±25.8 (0–157.5)†	17.7±22.2 (0–135)	23.1±37.8 (0–318)†	0.01†
PE/PP (%)	43.7	30.3*	40.7	0.02*
Intravenous Ig (%)	19.3	26.7	20.4	0.16
EFT (%)	31.4*	39.8*	53.6*	<0.0001*
Early use of CNIs (%)	12.2*	29.8*	47.1*	<0.0001*

EFT is use of fast-acting therapy such as PP, often combined with HMP, HMP alone or intravenous Ig within 6 months of treatment initiation.

*Pearson's X^2 test.

†Significant difference detected by one-way ANOVA followed by the Tukey-Kramer test.

ANOVA, analysis of variance; CNIs, calcineurin inhibitors; EFT, early fast-acting treatment; HMP, high-dose intravenous methylprednisolone; Ig, immunoglobulin; MGFA, Myasthenia Gravis Foundation of America; MM-or-better-5mg for ≥6 months, minimal manifestation status or better on prednisolone ≤5 mg/day lasting ≥6 months (the treatment target); PE, plasma exchange; PP, plasmapheresis; PSL, prednisolone; QMG, quantitative myasthenia gravis.

statistically significant. The JMP statistical program (SAS Institute, Cary, North Carolina, USA) was used for data analysis.

RESULTS

Differences in characteristics of patients classified by oral PSL dosing regimen

Of 590 patients, 237 were classified in the high-dose group, 187 in the intermediate-dose group and 166 in the low-dose group. The age of onset (high-dose group vs intermediate-dose group vs low-dose group: 42.3±16.8 vs 46.4±16.9 vs 51.1±19.4 years, P<0.0001), the rate of thymectomy (83.1% vs 65.8% vs 36.1%, P<0.0001) and the prevalence of thymoma (29.1% vs 38.5% vs 22.9%, P=0.006) were significantly different between any two of the three groups (table 1). Disease duration was significantly longer in the high-dose group (15.0±10.0 years, P<0.0001). The prevalence of AChRAb positivity was significantly lower in the low-dose group (76.0%, P=0.002). The current daily dose of PSL was significantly higher in the intermediate-dose group (7.1±5.8 mg, P<0.0001) compared with the other two groups, but not different between high-dose and low-dose groups (4.5±5.1 vs 4.8±3.2 mg). The daily dose of pyridostigmine was 58.2±79.4 mg in the high-dose group and was significantly lower (P=0.003) than 80.7±77.7 mg in the intermediate-dose group. The MuSKAb-positive rate, postintervention status, current combination of CNIs and daily dose of tacrolimus were not significantly different between any two of the three groups.

Maximum severity, achievement of status and other treatment in three groups classified by oral PSL dosing regimen

Pearson's X^2 test showed a significantly higher percentage of patients with maximum severity in the high-dose group compared with the other two groups (P<0.0001). ANOVA followed by Tukey-Kramer test also showed that the worst QMG score for the entire disease period was significantly higher (P<0.0001) in the high-dose group (18.6±7.9) than in the intermediate-dose group (14.4±6.4) or the low-dose group (13.9±6.3) (table 2). The proportion of patients who maintained MM-or-better-5mg for ≥6 months was significantly higher (P<0.0001) in the low-dose group than in the intermediate-dose or high-dose group during 3 years after treatment was started (low-dose group vs intermediate-dose group or high-dose group: 52.1% vs 11.4% or 9.6% after 1 year of treatment; 61.2% vs 30.8% or 29.9% after 2 years; 64.1% vs 36.4% or 44.1% after 3 years). Patients in the high-dose group received a smaller cumulative HMP dose compared with patients in the low-dose group (12.9±25.8 vs 23.1±37.8 g, P=0.01). Treatment with PE/PP was significantly infrequent (P=0.02) in the intermediate-dose group (30.3%) than in the high-dose group (43.7%) or the low-dose group (40.7%). The rates of combined EFT (31.4% in the high-dose group vs 39.8% in the intermediate-dose group vs 53.6% in the low-dose group) and early combined use of CNIs (12.2% in the high-dose group vs 29.8% in the intermediate-dose group vs 47.1% in the low-dose group) starting within 6 months of treatment were significantly different between any two of three groups (P<0.0001). The low-dose group showed remarkably higher rates of combined uses of EFT and CNIs.

Independent predictors for MM-or-better-5mg identified by multivariate logistic regression modelling

Multivariate logistic regression analysis identified low-dose regimen as the sole independent positive predictor to achieve MM-or-better-5mg for ≥6 months after 1 year of treatment (table 3). The ORs were 10.4 (95% CI 4.54 to 25.2, P<0.0001) for low-dose versus high-dose regimen and 13.4 (95% CI 5.69 to 34.8, P<0.0001) for low-dose versus intermediate-dose regimen. The analysis also identified EFT, early use of CNIs and low-dose regimen as significant independent positive predictors to achieve MM-or-better-5mg for ≥6 months after 2 and 3 years of treatment. The ORs (95% CI) were 2.19 (1.11 to 4.42) after 2 years (P=0.02) and 2.11 (1.03 to 4.44) after 3 years (P=0.04) for EFT; 2.09 (1.09 to 4.06) after 2 years (P=0.03) and 2.36 (1.13 to 5.09) after 3 years (P=0.02) for early use of CNIs; 2.75 (1.31 to 5.88) after 2 years (P=0.007) and 1.86 (0.79 to 4.49) after 3 years (P=0.15, not significant) for low-dose versus high-dose regimen; and 3.99 (1.86 to 8.81) after 2 years (P=0.0003) and 4.92 (2.00 to 12.6) after 3 years (P=0.0004) for low-dose versus intermediate-dose regimen. None of the other significant

Table 3 Independent predictors of MM-or-better-5mg for ≥6 months identified by multivariate logistic modelling

Parameters	OR (95% CI), P value		
	After 1 year	After 2 years	After 3 years
EFT	2.04 (0.89 to 4.78), 0.09	2.19 (1.11 to 4.42), 0.02*	2.11 (1.03 to 4.44), 0.04*
Early use of CNIs	1.59 (0.78 to 3.24), 0.20	2.09 (1.09 to 4.06), 0.03*	2.36 (1.13 to 5.09), 0.02*
Oral PSL dosing regimen			
Low-dose/high-dose	10.4 (4.54 to 25.2), <0.0001*	2.75 (1.31 to 5.88), 0.007*	1.86 (0.79 to 4.49), 0.15
Low-dose/intermediate-dose	13.4 (5.69 to 34.8), <0.0001*	3.99 (1.86 to 8.81), 0.0003*	4.92 (2.00 to 12.6), 0.0004*

The following variables were also entered in the multivariate logistic model: demographics, antibody status, thymus status, pyridostigmine use, MGFA postintervention status, worst QMG score, accumulated dose of HMP, PE/PP and Ig. Factors that did not show significance after being run through the model are not shown.

EFT is use of fast-acting therapy such as PP, often combined with HMP, HMP alone or intravenous Ig within 6 months of treatment initiation.

*An independent predictor to achieve the treatment target.

CNIs, calcineurin inhibitors; EFT, early fast-acting treatment; HMP, high-dose intravenous methylprednisolone; Ig, immunoglobulin; MGFA, Myasthenia Gravis Foundation of America; MM-or-better-5mg for ≥6 months, minimal manifestation status or better on PSL ≤5 mg/day lasting >6 months (the treatment target); PE/PP, plasma exchange/plasmapheresis; PSL, prednisolone; QMG, quantitative myasthenia gravis.

variables identified in univariate analyses and entered into the logistic regression model (including age of onset, disease duration, antibody status, thymus status, pyridostigmine use, HMP, PE/PP, intravenous Ig and worst QMG score) were found to independently predict achievement of MM-or-better-5mg for ≥6 months.

DISCUSSION

Oral corticosteroids have not been a subject of controlled clinical trial for a long time.[16] A previous report suggests that nearly 10% of patients with generalised MG achieve complete remission in spite of the therapeutic environment and that some patients with MG may be good responders to any treatment.[2] Even in the recent consensus guidance for management of MG,[9] the panel did not explicitly address chronic MG management, which generates the most common questions from patients: 'how long should I take steroids, and at what doses?'.[17] The present study provides class IV evidence, and our multivariate logistic regression analysis identified low-dose regimen of oral PSL as a positive predictor of maintaining the favourable status of MM-or-better-5mg for ≥6 months (treatment goal). In a previous domestic survey, we already reported that high-dose regimen of oral PSL did not correlate with achievement of a MM-or-better status.[12] The present results further show that low-dose regimen of oral PSL is superior to high-dose and intermediate-dose regimens in maintaining the treatment goal for 2 and 3 years, respectively. After 1 year of treatment, <10% of high-dose patients compared with >50% of low-dose patients achieved MM-or-better-5mg for ≥6 months (table 2), probably in part due to the difficulty of reducing the dose to 5 mg in the high-dose group. The OR for low dose versus high dose in achieving treatment goal remained significantly high even after 2 years of treatment, although the OR lost statistical significance after 3 years, showing a tendency of convergence (table 3). After 3 years, no differences in the rate of MM status and current treatments including daily PSL dose were observed between the two groups (table 1). On the other hand, the low-dose versus intermediate-dose OR for achieving treatment goal remained significantly high even after 3 years of treatment (table 3). The present findings thus show that low-dose regimen may accomplish the treatment target earlier and maintain the favourable status more effectively than higher-dose regimens.

Furthermore, our data suggest a possible role of low-dose regimen to suppress symptom aggravation through the entire course of disease. We analysed the maximum severity during the entire disease by analysing the worst MGFA clinical classification

and worst QMG score in patients classified by PSL dosing regimen, but these values did not necessarily reflect the severity at the beginning of treatment. Therefore, lower maximum severity based on these assessments observed in the low-dose regimen group did not always indicate that these patients had less severe disease at the beginning of treatment, but may suggest that low-dose regimen possibly suppresses disease aggravation. Indeed, the low-dose group had very low rates of grades IV and V compared with the other two groups (table 2).

Our results also identified early combination of fast-acting treatment or CNIs as a positive predictor for accomplishing treatment target, irrespective of the PSL dosing regimen. While immunotherapy is probably more effective against MG during the earlier stages of disease,[12 15 18] early achievement of treatment goal possibly leads to better long-term outcome. The proportion of patients who started EFT and/or CNIs within 6 months of treatment was higher in those receiving low-dose regimen of oral PSL. In addition, EFT and early combined use of CNIs were positive predictive factors to achieve MM-or-better-5mg for ≥6 months at 2 and 3 years after starting of MG treatment (table 3). The most important point may be 'early' combined use of these treatment options. The Japanese clinical guidelines for MG recommend that the use of CNIs (ciclosporin and tacrolimus) in patients with shorter disease duration.[8] This may be reflected by the much higher rates of early use of CNIs in the low-dose group (with shorter disease duration than high-dose group), presumably with expectation of their steroid-sparing effects.[19] Previous surveys recommended that the PSL dose should be decreased by combining with modalities such as PE/PP or intravenous Ig[20–22] when MM-or-better is not achieved at a maximum PSL dose.[12] However, PE/PP and intravenous Ig generally are not considered as maintenance therapy to maintain a favourable state (such as MM-or-better-5mg as the treatment target in the Japanese clinical guidelines). In fact, the rates of PE/PP and intravenous Ig were not significantly different between the high-dose and low-dose groups (table 2), and PE/PP and intravenous Ig were not identified as independent predictors of achieving MM-or-better-5mg for ≥6 months in logistic regression analysis (data not shown). Also, the rate of CNI cotreatment at the time of the study was not significantly different between three groups with different oral PSL dosing regimens (table 1), and current CNI cotreatment had no significant effect on achieving a favourable status in multivariate logistic regression modelling (data not shown). Nagane et al[18] reported that disease severity, daily dose of PSL and AChRAb level were reduced following CNI treatment, and suggested that poor CNI responders may

be the result of alterations in immunopathological conditions during long-term disease or longer and more severe disease than that in responders. Therefore, CNI should be given to patients with factors known to enhance susceptibility to these drugs, such as early-stage disease.[23]

On the other hand, the accumulated dose of HMP[24] was significantly higher in the low-dose group than in the high-dose group. The low-dose regimen was often combined with the other treatment options including HMP. Although HMP is also a steroid therapy, we regard HMP as one of the fast-acting therapies to achieve a favourable status using the lowest possible dose of oral PSL. It makes clinical sense that HMP should be used to obtain early clinical response by its rapid actions.

Multivariate logistic regression analysis detected no significant variables from demographics, antibody status and thymus status, which predict MM-or-better-5mg for ≥6 months. However, we recognised considerable differences in characteristics of patients among the dosing regimen groups (table 1). The low-dose group had older onset age, shorter disease duration, higher AChRAb-negative rate and lower thymectomy rate. These data suggest that low-dose regimen tends to be used in more recent patients, because low-dose regimen is often combined with CNIs and intravenous Ig and these agents for generalised MG have been covered by the Japanese health insurance system only in recent years (tacrolimus in 2000, ciclosporin in 2006 and intravenous Ig in 2011). The higher AChRAb-negative rate may reflect recent improvement of diagnosis tests for seronegative MG, and the lower thymectomy rate may reflect the changing opinion on indication of thymectomy as described in the Japanese clinical guidelines for MG.[8] Additionally, recent studies suggest that higher PSL dose is not always superior to relatively low PSL doses (such as 20 mg/day) combined with other treatment options.[11 25]

There is no internationally accepted standard treatment regimen for MG, including that for oral PSL, partly because MG is heterogeneous and no one treatment approach is best for all patients.[9] However, we believe this nationwide survey provides useful information for MG patients, in spite of several limitations including the retrospective and unblinded design. We did not collect the data on the cost for each dosing regimen in this survey. However, we expect that most patients would prefer low-dose PSL with early combination of other modalities to achieve the treatment target earlier, possibly with little symptom aggravation and less adverse effects, even if the cost is higher than high-dose PSL with an escalation and de-escalation schedule.

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REFERENCES

1 Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. *Ann Neurol* 1984;15:291–8.
2 Grob D, Brunner N, Namba T, *et al*. Lifetime course of myasthenia gravis. *Muscle Nerve* 2008;37:141–9.
3 Gilhus NE. Autoimmune myasthenia gravis. *Expert Rev Neurother* 2009;9:351–8.
4 Sanders DB, Evoli A. Immunosuppressive therapies in myasthenia gravis. *Autoimmunity* 2010;43:428–35.
5 Masuda M, Utsugisawa K, Suzuki S, *et al*. The MG-QOL15 Japanese version: validation and associations with clinical factors. *Muscle Nerve* 2012;46:166–73.
6 Jaretzki A, Barohn RJ, Ernstoff RM, *et al*. Myasthenia gravis: recommendations for clinical research standards. Task force of the medical scientific advisory board of the myasthenia gravis foundation of america. *Neurology* 2000;55:16–23.
7 Utsugisawa K, Suzuki S, Nagane Y, *et al*. Health-related quality-of-life and treatment targets in myasthenia gravis. *Muscle Nerve* 2014;50:493–500.
8 Murai H. Japanese clinical guidelines for myasthenia gravis: putting into practice. *Clinical and Experimental Neuroimmunology* 2015;6:21–31.
9 Sanders DB, Wolfe GI, Benatar M, *et al*. International consensus guidance for management of myasthenia gravis: executive summary. *Neurology* 2016;87:419–25.
10 Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *Lancet Neurol* 2009;8:475–90.
11 Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. *Neurology* 2008;71:394–9.
12 Imai T, Suzuki S, Tsuda E, *et al*. Oral corticosteroid therapy and present disease status in myasthenia gravis. *Muscle Nerve* 2015;51:692–6.
13 Kokubun N, Sonoo M, Imai T, *et al*. Reference values for voluntary and stimulated single-fibre EMG using concentric needle electrodes: a multicentre prospective study. *Clin Neurophysiol* 2012;123:613–20.
14 Utsugisawa K, Nagane Y, Akaishi T, *et al*. Early fast-acting treatment strategy against generalized myasthenia gravis. *Muscle Nerve* 2017;55:794–801.
15 Nagane Y, Suzuki S, Suzuki N, *et al*. Early aggressive treatment strategy against myasthenia gravis. *Eur Neurol* 2011;65:16–22.
16 Rowland LP. Controversies about the treatment of myasthenia gravis. *J Neurol Neurosurg Psychiatry* 1980;43:644–59.
17 Dalakas MC. Treating myasthenia on consensus guide: helpful and challenging but still unfinished business. *Neurology* 2016;87:350–1.
18 Nagane Y, Suzuki S, Suzuki N, *et al*. Factors associated with response to calcineurin inhibitors in myasthenia gravis. *Muscle Nerve* 2010;41:212–8.
19 Yoshikawa H, Kiuchi T, Saida T, *et al*. Randomised, double-blind, placebo-controlled study of tacrolimus in myasthenia gravis. *J Neurol Neurosurg Psychiatry* 2011;82:970–7.
20 Barth D, Nabavi Nouri M, Ng E, *et al*. Comparison of IVIg and PLEX in patients with myasthenia gravis. *Neurology* 2011;76:2017–23.
21 Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. *Neurology* 2007;68:837–41.
22 Gajdos P, Chevret S, Clair B, *et al*. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. *Ann Neurol* 1997;41:789–96.
23 Utsugisawa K, Nagane Y, Imai T, *et al*. Treatment of myasthenia gravis patients with calcineurin inhibitors in Japan: a retrospective analysis of outcomes. *Clinical and Experimental Neuroimmunology* 2015;6:195–200.
24 Lindberg C, Andersen O, Lefvert AK. Treatment of myasthenia gravis with methylprednisolone pulse: a double blind study. *Acta Neurol Scand* 1998;97:370–3.
25 Wolfe GI, Kaminski HJ, Aban IB, *et al*. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med* 2016;375:511–22.