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ORIGINAL ARTICLE

Clinical burden and healthcare resource utilization associated with myasthenia gravis: Assessments from a Japanese claims database

Hiroyuki Murai,[1] Miki Hasebe,[2] Tatsunori Murata[3] and Kimiaki Utsugisawa[4]

[1]Department of Neurology, International University of Health and Welfare, [2]Medical Affairs, Alexion Pharma, [3]CRECON Medical Assessment, Tokyo, [4]Department of Neurology, Hanamaki General Hospital, Iwate, Japan

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Correspondence
Miki Hasebe, PhD, Medical Affairs, Alexion Pharma GK, Tokyo, Japan, 1-18-14 Ebisu, Shibuya-ku, Tokyo 150-0013, Japan.
Tel: +81-3-5795-0805
Fax: +81-3-5795-0767
Email: miki.hasebe@alexion.com

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Abstract

Objectives To compare the burden of illness for refractory and non-refractory myasthenia gravis (MG) in Japanese patients.

Methods Adults in a large Japanese health insurance claims database (1 September 2008 to 31 October 2016) were included in this retrospective, observational study if they had: at least two separate claims coded as MG by a neurologist; and continuous enrollment for 12 months after any MG claim (non-refractory cohort) or the earliest claim associated with refractory disease (refractory cohort). A cohort with Parkinson's disease was used as the reference for the burden of illness of MG, and comprised patients matched (sex, age and index date) to patients with MG. Outcomes included respiratory failure, myasthenic exacerbations, outpatient hospital and emergency room visits, and hospitalizations.

Results A significantly greater proportion of the refractory cohort (n = 165) than the non-refractory cohort (n = 3137) experienced respiratory failure (17.0% *vs* 5.5%, respectively; $P < 0.001$) and/or exacerbations (57.6% *vs* 5.8%, respectively; $P < 0.001$) over 12 months. The mean numbers of hospitalizations (0.68 *vs* 0.09/year), emergency room visits (0.07 *vs* 0.03/year) and outpatient hospital visits (16.79 *vs* 11.88/year), and the mean duration of hospital stays (22.19 *vs* 2.81 days/year) were also significantly greater for the refractory cohort (all $P < 0.001$). Except for emergency room visits, healthcare resource utilization was significantly greater for non-refractory MG than for Parkinson's disease (n = 3168).

Conclusions In Japanese patients, refractory MG is associated with a greater clinical burden and healthcare resource utilization than non-refractory MG.

Introduction

Although myasthenia gravis (MG) is the most common disorder of neuromuscular transmission, it is considered a rare autoimmune disease.[1] In Japan, data from 2006 suggest that MG affects an estimated 11.8 individuals per 100 000.[2] This sometimes affects only ocular muscles (ocular MG), but the problems are often more widespread. In the latter case, patients might experience difficulties with talking, chewing, swallowing, cervical muscle weakness (head drop), limb weakness and/or respiratory problems. Serious exacerbations can cause life-threatening dysphagia and respiratory muscle weakness, with the latter leading to the need for intubation and/or mechanical ventilation. In fact, it is estimated that 15–20% of patients experience respiratory failure (myasthenic crisis).[3] Traditional therapies, including acetylcholinesterase inhibitors and immunomodulating therapies (such as corticosteroids, azathioprine and mycophenolate mofetil), often allow patients to lead productive lives with few or no symptoms. Furthermore, with effective treatment, mortality has decreased over several decades from 75% to 4.5%.[3]

Notwithstanding overall improvements in the clinical outlook associated with MG, approximately

10–15% of patients are estimated to have refractory (difficult-to-treat) disease.[3,4] Refractory MG is typically understood to be present if the disease is not clinically controlled with immunotherapy used in adequate doses for an adequate duration, with persistent symptoms or side-effects that limit functioning.[3,5,6] Patients with severe disease are likely to remain at risk of serious exacerbations, which is of particular concern in light of research suggesting that there have been only modest improvements in mortality among hospitalized patients with MG requiring mechanical ventilation.[7]

Characterizing the burden of illness in refractory MG will help to inform the unmet need in this difficult-to-treat population. A few studies have assessed the clinical burden and utilization of healthcare resources associated with MG.[8–11] Of particular interest is the research by Engel-Nitz *et al*., who used USA medical and pharmacy claims data and enrollment information from two administrative health plan databases, the Optum Research Database and Impact National Benchmark Database, to focus on the subset of patients refractory to conventional treatment.[11] The authors concluded that a significantly greater proportion of patients with refractory MG than non-refractory MG experienced at least one myasthenic crisis and at least one exacerbation over a 1-year period.[11] Additionally, patients with refractory MG were significantly more likely to be hospitalized and/or visit an emergency room than those with non-refractory disease. It is currently unclear whether similar conclusions about clinical burden and utilization of healthcare resources can be drawn for Japanese patients with refractory MG, because the medical systems in the USA and Japan differ significantly.

Parkinson's disease (PD) is a chronic, progressive and disabling neurological disorder affecting approximately 108 800 people in Japan.[12] Although there are no meaningful biomarkers and surrogate markers for diagnosis, PD is commonly treated by Japanese neurologists, and a definitive diagnosis is well established. The burden of illness associated with PD thus potentially serves as a useful comparator for the burden of illness associated with MG.

The primary objective of the present study was to compare the clinical burden and utilization of healthcare resources in patients with either refractory MG or non-refractory MG using data from a Japanese health insurance claims database. To contextualize findings, the utilization of healthcare resources in non-refractory MG was also compared with that in patients with PD.

Methods

Study design and data source

This was a retrospective, observational study undertaken using anonymized health records from an electronic database provided by Medical Data Vision (Tokyo, Japan). This is the largest commercial source of health records in Japan, containing medical and prescription data relating to inpatient and outpatient health insurance claims from 279 hospitals (as of August 2016) and approximately 16.3 million patients. Each prescription record comprises drug name, dose, prescription date, code number for the drug formulation and the number of days of medication prescribed. The health records available for the study were from 1 September 2008 to 31 October 2016 (study period); data for patients with MG or PD were extracted from these records on 22 March 2017 and 17 November 2017, respectively. Patients in the database are classified according to diagnosis and then type of procedure (diagnostic procedure combination classification) for medical service claims. As of 2014, 21% of the general hospitals in Japan (representing 55% of beds used for general admissions across all hospitals) had adopted the diagnostic procedure combination classification. The database additionally provides background information about patients, such as sex, age and the medical practices attended.

Study populations

Patients with MG were included in the study if they: (i) had been enrolled in the database during the study period; (ii) had at least two claims on separate dates within this period, each with a diagnosis code for MG (G70.0; from the 10th revision of the International Statistical Classification of Diseases and Related Health Problems[13]), and each with neurology listed as the healthcare provider's specialty; (iii) were aged ≥18 years on the index date (defined below); and (iv) had continuous enrollment for at least 12 months after the index date. Patients were excluded from the study if the MG diagnosis was potentially for the purpose of treating any of the 20 other diseases (e.g. multiple sclerosis, neuromyelitis optica and chronic inflammatory demyelinating polyneuropathy; the list of diseases for which patients were excluded is shown in Table S1).

Patients with MG were divided into two cohorts: refractory and non-refractory. For the purpose of this research using a claims database (in which there are no data regarding disease severity), refractory

MG was considered to be present if patients had used at least three immunosuppressive therapies (azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus or oral corticosteroids) within a 24-month period. Alternatively, refractory disease was considered to be present if patients were prescribed, on the same day, at least one immunosuppressive therapy and at least one therapy (cyclophosphamide or rituximab) typically reserved for MG that is resistant to conventional therapies, or if they had been prescribed at least one immunosuppressive therapy and had at least three claims for treatment with plasmapheresis (PP) or intravenous immunoglobulin (IVIg) on separate dates within a 12-month period. A 24-month period was allowed for the use of at least three immunosuppressive therapies to ensure sufficient time for sequential progression through treatment options. The index date for a patient with refractory MG was the earliest date associated with any of the criteria for refractory disease. The non-refractory cohort included all enrolled patients with MG whose disease was not identified as refractory. The index date for patients with non-refractory MG was the date of the first claim associated with MG during the study period.

Patients in the PD cohort were required to have no medical claims with diagnosis codes for MG at any time during the study period. Patients were additionally required to have continuous enrollment in the database for at least 24 months, with enrollment for at least 12 months after the index date (≥12 months, but <24 months of continuous enrollment after the index date in the case of patients who had died). Patients were excluded from the cohort if they could not be matched (based on sex, age and index date) to a patient in the overall MG cohort. The index date for patients with PD was the date of the first claim associated with PD during the study period.

Outcome measures

Demographic characteristics at the index date and clinical characteristics during the 12 months after the index date were collated to understand the background of the study population. Corticosteroid use was described in terms of the proportion of patients prescribed corticosteroids at any time in the 12 months after the index date, the initial doses prescribed (during the 90 days after the index date) and the dose changes over the 12 months after the index date. Initial doses and dose changes were converted to prednisolone-equivalent doses to facilitate pooling of data within the MG cohorts and comparisons between them. Changes in dosing were expressed as relative dose intensities (RDI), calculated using the equation below. RDI >1 indicate increasing doses.

$$\mathrm{RDI} = \frac{\text{actual cumulative total corticosteroid dose converted into prednisolone dose for the 12-month period after the index date}}{\text{daily corticosteroid dose specified in the first prescription at the first visit during the 90 days after the index date} \times 365\text{days}}$$

Clinical burden and the utilization of healthcare resources were measured for the 12-month period after the index date. The measures for clinical burden were the proportions of patients experiencing respiratory failure and myasthenic exacerbations. Myasthenic exacerbations were defined as intubation/ventilation, dysphagia, or treatment with PP or IVIg. The outcome measures for the utilization of healthcare resources were: number of outpatient hospital visits, emergency room visits and hospitalizations; and the total duration of hospital stays. The number of hospitalizations and the total duration of hospital stays were restricted to MG-related hospitalizations for the MG cohort and to PD-related hospitalizations for the PD cohort, each using diagnostic procedure combination classification records. The likelihoods of patients experiencing at least one hospitalization, emergency room visit, respiratory failure or MG exacerbation in the refractory MG cohort were compared with those in the non-refractory MG cohort. To assess the specific burden associated with intensive therapy in the refractory MG group, utilization of healthcare resources was compared for patients who had at least three claims for PP and/or IVIg, and for those who had fewer claims in the 12-month period after the index date.

Statistical analysis

Descriptive statistics were calculated for demographic and clinical characteristics, use of corticosteroids,

clinical events, and utilization of healthcare resources. Differences between cohorts were examined using χ^2-tests (categorical variables) and analyses of variance (continuous variables). Logistic regression models adjusted for age (in 10-year intervals), sex, Quan–Charlson comorbidity score (calculated from the 10th revision of the International Statistical Classification of Diseases and Related Health Problems diagnosis codes associated with claims in the health records),[14] and history of autoimmune disorders, diabetes and hypertension were used to compare the likelihood of patients in the refractory MG cohort experiencing at least one respiratory failure, MG exacerbation, hospitalization or emergency room visit, compared with patients in the non-refractory MG cohort.

Results

A total of 10 297 patients had at least one claim relating to an MG diagnosis code during the study period (Fig. 1). Of these, 3302 patients met the inclusion criteria for the study (refractory MG cohort, $n = 165$; non-refractory MG cohort, $n = 3137$). A further 3168 patients with PD in the database were included in the PD cohort.

Approximately 60% of each cohort were women (Table 1). The refractory MG cohort was younger than the non-refractory MG cohort, and had higher comorbidity rates for thymoma, diabetes (excluding type 1 disease), hypertension and autoimmune disease. Almost all patients in the refractory MG cohort were prescribed corticosteroids compared with just over half of the non-refractory MG cohort. The daily doses and RDI of corticosteroids prescribed were significantly higher for patients with refractory MG than for those with non-refractory MG (Table 2). Additionally, a significantly greater proportion of the non-refractory MG cohort than of the refractory MG cohort had their doses reduced, and a significantly smaller proportion of the non-refractory MG group had their doses increased during the 12 months after the index date. The distribution of RDI across the two cohorts is shown in Fig. 2.

Compared with the patients with non-refractory MG, those with refractory disease had a significantly higher clinical burden (rates of respiratory failure and myasthenic exacerbations; Table 3) and utilization of healthcare resources (number and duration of hospital stays, and number of emergency room and outpatient hospital visits; Table 4). Similar results were obtained after adjusting data for patient age, sex, Quan–Charlson comorbidity score, and history of autoimmune disorders, diabetes and hypertension (Table 5).

Except for emergency room visits, utilization of healthcare resources was significantly higher in the non-refractory MG cohort than in the PD cohort (Table 4).

For patients with refractory MG, the mean number of hospitalizations and the mean total duration of hospital stays were significantly higher among those with at least three claims in 1 year for treatment with PP and/or IVIg than among those with fewer claims (Table 6). Differences between the two groups were not significant for the mean number of

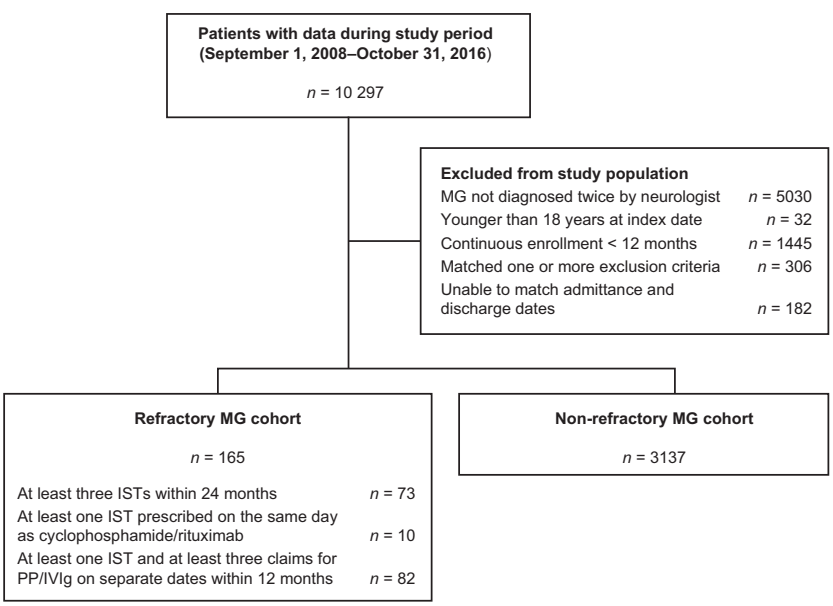

Figure 1 Flow diagram for patients with myasthenia gravis (MG) assessed for inclusion in the study. IST, immunosuppressive therapy; IVIg, intravenous immunoglobulin; PP, plasmapheresis.

Table 1 Demographic and clinical characteristics of the myasthenia gravis and Parkinson's disease cohorts

	Refractory MG cohort (n = 165)	Non-refractory MG cohort (n = 3137)	PD cohort (n = 3168)
Women	103 (62.4)	1859 (59.3)	1872 (59.1)
Age at index date (years)			
Mean ± SD	56.9 ± 14.98	62.1 ± 15.49	62.0 ± 15.44
History of disease			
Thymoma	37 (22.4)	422 (13.5)	0
Diabetes (type 1 excluded)	116 (70.3)	1513 (48.2)	656 (20.7)
Hypertension	78 (47.3)	1120 (35.7)	964 (30.4)
Autoimmune disease	102 (61.8)	1374 (43.8)	772 (24.4)
Quan–Charlson comorbidity score			
Mean ± SD	2.8 (2.88)	1.8 (2.11)	1.4 (2.02)
Thymectomy†	9 (5.5)	45 (1.4)	0
Antibody testing†			
AChR	141 (85.5)	2281 (72.7)	19 (0.6)
MuSK	14 (8.5)	149 (4.7)	1 (0.0)
Corticosteroid use	163 (98.8)	1608 (51.3)	278 (8.8)

Data are number (%) of patients, unless stated otherwise; data were collected during the 12 months after the index date, unless stated otherwise. †As procedures from previous hospitals were not recorded in the database, the true number of patients might be underestimated. AChR, acetylcholine receptor; MG, myasthenia gravis; MuSK, muscle-specific tyrosine kinase; PD, Parkinson's disease; SD, standard deviation.

Table 2 Initial daily doses and relative dose intensities of corticosteroids prescribed for myasthenia gravis cohorts

	Refractory MG cohort (n = 151)	Non-refractory MG cohort (n = 1370)	P-value
Initial daily corticosteroid doses†			
Mean ± SD (mg)	15.21 ± 13.91	12.31 ± 12.24	0.007
Corticosteroid RDI‡			
Mean ± SD	1.16 ± 1.19	0.79 ± 0.65	<0.001
RDI <0.8, n (%)	59 (39.1)	779 (56.9)	<0.001
0.8 ≤ RDI ≤ 1.1, n (%)	46 (30.5)	452 (33.0)	0.530
RDI >1.1, n (%)	46 (30.5)	139 (10.1)	<0.001

Corticosteroid doses have been converted to oral prednisolone-equivalent doses to facilitate pooling of data within, and comparisons between, myasthenia gravis (MG) cohorts.
†During the 90 days or the ‡12 months following the index date. RDI, relative dose intensity; SD, standard deviation.

visits to emergency rooms or the mean number of hospital outpatient visits.

Discussion

This is one of the first large, population-based studies to evaluate the burden of illness, in terms of clinical burden and healthcare resource utilization, in Japanese patients with MG. Patients with non-refractory MG showed significantly higher healthcare resource utilization (except for the frequency of emergency room visits) than patients with PD. When comparing the Quan–Charlson comorbidity score as a predictor of the 10-year mortality for a patient, the score (mean 1.8 [SD 2.11]) in the non-refractory MG cohort tends to be higher than that (mean 1.4 [SD 2.02]) in the PD cohort. These findings suggest that the non-refractory MG patients showed somewhat complicated or severe conditions, which might be at least in part caused by various side-effects from long-term oral steroids frequently used against MG. Among patients with MG, those with refractory disease were prescribed higher doses of corticosteroids, had a greater clinical burden and had a higher utilization of healthcare resources than those with non-refractory disease. Additionally, patients with refractory MG tended to be younger than those with non-refractory MG, and there might therefore be a greater impact on their contributions to family and society.

Imai *et al*. showed that higher doses of, and longer treatment with, corticosteroids do not ensure better outcomes in patients with MG.[15] Furthermore, many patients and physicians are motivated to taper doses to reduce the complications associated with high doses of oral corticosteroids, such as mood problems.[16,17] However, higher doses and the longer-term use of corticosteroids still persist in clinical practice. During the 12 months after the index date in the present study, most patients did in fact have their doses reduced. This happened for a greater proportion of the non-refractory MG cohort than of the refractory MG cohort. As the latter also had significantly higher corticosteroid doses at the index date, this suggests that patients with refractory MG carry a greater burden of treatment complications from corticosteroid therapy than those with non-refractory disease.

In a USA study, the refractory MG cohort had higher rates of respiratory failure and MG exacerbations throughout the disease course than the non-refractory MG cohort.[11] This is likely to have contributed to the higher rates of hospitalizations and emergency room visits in the refractory cohort. A similar tendency was apparent in the present study despite significant differences in the medical systems between the USA and Japan. Taken together, these two reports highlight the need for new treatment options for this difficult-to-treat population.

In the refractory MG cohort in the present study, patients with frequent prescriptions for PP and/or

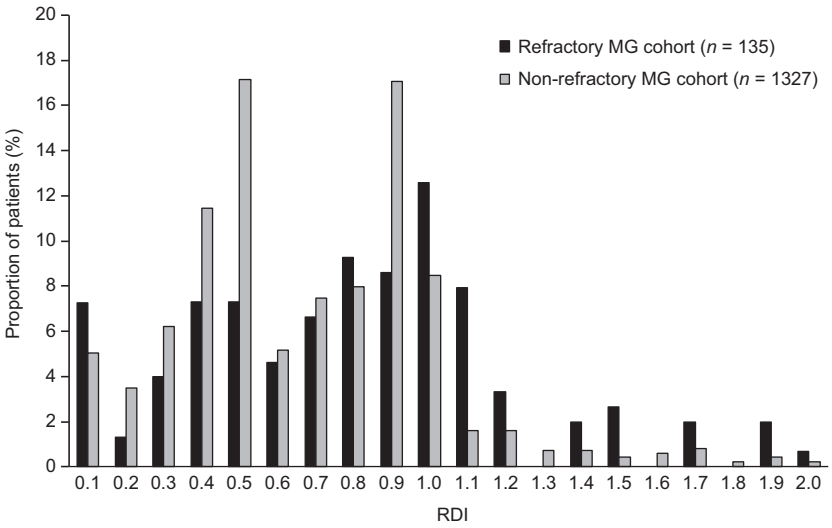

Figure 2 Distribution of relative dose intensities for corticosteroids. Data are shown only for patients with relative dose intensities (RDI) ≤2.0; 16 patients (10.6%) in the refractory myasthenia gravis (MG) cohort and 43 patients (3.1%) in the non-refractory MG cohort had RDI >2.0. Corticosteroid doses have been converted to oral prednisolone-equivalent doses to facilitate pooling of data within, and comparisons across, MG cohorts.

Table 3 Clinical events occurring in myasthenia gravis cohorts

	Refractory MG cohort (*n* = 165)	Non-refractory MG cohort (*n* = 3137)	*P*-value
Respiratory failure	28 (17.0)	171 (5.5)	<0.001
Myasthenic exacerbation	95 (57.6)	183 (5.8)	<0.001
Intubation/ventilation	12 (7.3)	16 (0.5)	<0.001
Dysphagia	32 (19.4)	126 (4.0)	<0.001
Plasma exchange	71 (43.0)	20 (0.6)	<0.001
IVIg	47 (28.5)	60 (1.9)	<0.001

Data are number (%) of patients experiencing a clinical event during the 12 months after the index date. IVIg, intravenous immunoglobulin; MG, myasthenia gravis.

IVIg (i.e. at least three claims for these treatments in 12 months) had a significantly greater number of hospitalizations and significantly longer durations of hospital stays than patients with fewer claims (although the number of visits as hospital outpatients or to emergency rooms were not significantly different). These data suggest that refractory disease greatly impairs the quality of life of this subgroup of patients. The societal burden of MG was not part of the present study, but it is possible that the relatively long hospital stays in the cohort with at least three claims of PP/IVIg in a year (mean 32.3 [SD 37.2] days, compared with 12.2 [26.2] days) for those with fewer than three claims, in the 12 months preceding the index date, might interfere with the demands of employment. A multicenter, cross-sectional study carried out in 2015 showed that 185 of 680 patients with MG (27.2%; not specifically refractory disease) reported experiencing unemployment, yet the unemployment rate in the general population of Japan at the time was 3–4%.[18] Addressing the unmet medical needs of patients with MG, and of those with refractory disease in particular, thus has the potential to alleviate some of the constraints on non-clinical aspects of patients' lives.

The present study had several potential limitations. First, patients with ocular MG could not be excluded from the analysis, because they are commonly treated by neurologists rather than by ophthalmologists in Japan. These patients are likely to have been included in the non-refractory MG cohort and might have reduced the overall healthcare resource utilization and clinical burden in that cohort. Despite this limitation, patients with non-refractory MG were nonetheless admitted to hospital more frequently and for longer durations than patients with PD, underscoring the considerable burden of illness associated with MG, even when it is not refractory. Second, as noted also by Engel-Nitz *et al.*,[11] the use of a diagnostic code in the database does not prove that the disease was present. The diagnosis might have been incorrectly coded or the code might have represented a disease yet to be ruled out. To minimize the impact of this, however, patients were required to have at least two claims with a diagnosis code for MG from a neurologist on separate dates to be included in the MG study population. Third, patients with newly diagnosed MG could not be distinguished from those who had had the disease for many years, and some of the patients in the non-refractory MG cohort might have had refractory disease, but had not received the therapeutic interventions necessary to meet the criteria

Table 4 Utilization of healthcare resources in myasthenia gravis and Parkinson's disease cohorts

	Refractory MG cohort (n = 165)	Non-refractory MG cohort (n = 3137)	PD cohort (n = 3168)	*P*-value: Non-refractory MG *vs* refractory MG	*P*-value: PD *vs* non-refractory MG
No.:					
Hospitalizations	0.68 ± 0.91	0.09 ± 0.33	0.04 ± 0.24	<0.001	0.005
Emergency room visits	0.07 ± 0.28	0.03 ± 0.18	0.08 ± 0.33	0.002	0.718
Hospital outpatient visits	16.79 ± 9.90	11.88 ± 8.46	10.18 ± 15.78	<0.001	<0.001
Total duration of hospital stays (days)	22.19 ± 33.58	2.81 ± 12.90	0.97 ± 7.12	<0.001	<0.001

Data are mean ± SD for the 12-month period after the index date. MG, myasthenia gravis; PD, Parkinson's disease; SD, standard deviation.

Table 5 Adjusted odds ratios for experiencing at least one clinical event, hospitalization or emergency room visit for the refractory myasthenia gravis cohort compared with the non-refractory myasthenia gravis cohort

	Odds ratio	Lower 95% CI	Upper 95% CI	*P*-value
Respiratory failure	2.511	1.557	3.932	<0.001
Myasthenic exacerbation	19.525	13.655	28.081	<0.001
Hospitalization	9.636	6.699	14.076	<0.001
Emergency room visit	2.279	1.090	4.369	0.019

Data are from logistic regression models adjusted for age (in 10-year intervals), sex, Quan–Charlson comorbidity score, and history of autoimmune disorders, diabetes and hypertension. CI, confidence interval; MG, myasthenia gravis.

Table 6 Duration of hospital stays and number of emergency room visits according to healthcare claims for plasmapheresis and/or intravenous immunoglobulin in the refractory myasthenia gravis cohort

	Patients with:		
	At least three claims (n = 82)	Fewer than three claims (n = 83)	*P*-value
No.:			
Hospitalizations	1.06 ± 1.05	0.30 ± 0.53	<0.001
Emergency room visits	0.11 ± 0.35	0.04 ± 0.19	0.095
Hospital outpatient visits	16.12 ± 11.26	17.45 ± 8.37	0.392
Duration of hospital stays (days)	32.3 ± 37.2	12.2 ± 26.2	<0.001

Data are mean ± SD for the 12-month period after the index date. IVIg, intravenous immunoglobulin; MG, myasthenia gravis; PP, plasmapheresis; SD, standard deviation.

used in the study. These limitations are inherent in studies using claims databases, in which the medical history of patients is not complete, and the information captured is limited to that present in database health records during the study period. Fourth, the presence of a claim for a filled prescription does not guarantee that the medication was taken or that it was used as prescribed. Finally, although PP/IVIg therapy is a common treatment for patients with refractory MG, and was thus included in the criteria for identifying refractory disease, it was not possible to distinguish PP/IVIg used as a rescue therapy, maintenance treatment or as early fast-acting therapy at disease onset.

In conclusion, Japanese patients with refractory MG have a significantly greater clinical burden and higher rates of healthcare resource utilization than those with non-refractory MG. The burden of illness might be significant in light of the young age of many patients with refractory MG.

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Conflict of Interest

M.H. is an employee of Alexion Pharma, and author T.H. is an employee of CRECON Medical Assessment. H.M. and K.U. have received remuneration for consultancy services to Alexion. CRECON Medical Assessment prepared the study protocol, carried out the analyses and wrote the first draft of the manuscript (funded by Alexion Pharma).

Disclosure of ethical statement

No human participant was involved in this study.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1 Diseases for which patients were excluded from the study.