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Treatment Patterns and Disease Burden of Juvenile Myasthenia Gravis in the United States

A Cohort Study Using Health Care Claims Databases

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Abstract

Background and Objectives

Juvenile myasthenia gravis (JMG) is a rare disorder defined as MG in patients younger than 18 years. Generalized JMG is more common in postpubertal than prepubertal patients. There are no formal international JMG treatment guidelines, and knowledge on treatment patterns and disease burden is limited. The aim of this study was to describe treatment patterns and health care resource utilization (HCRU) for patients with JMG and explore differences in disease presentation between prepubertal-onset (younger than 12 years) and postpubertal-onset (12–17 years) patients.

Methods

Patients with JMG, newly diagnosed from 2008 to 2021, were identified from the US Merative MarketScan® Research Databases. Patients were followed from the first JMG claim (diagnosis/treatment with acetylcholinesterase inhibitors, immunoglobulin [Ig], or plasma exchange [PLEX]). The primary outcome was JMG-related treatment changes during follow-up, assessed descriptively. Rates of MG exacerbation, thymectomy, and acute intravenous immunoglobulin/PLEX treatment were assessed. HCRU was evaluated.

Results

A total of 630 patients (64.1% female; mean [SD] age 9.07 [5.73] years; 57.6% prepubertal onset) were followed for a median (range) of 2.4 (0–13) years. Corticosteroids were started at a median (range) of 1.28 (0–37.02) and 3.19 (0–87.68) months from diagnosis for postpubertal-onset and prepubertal-onset patients, respectively. The rate of thymectomy was highest during treatment with maintenance Ig/PLEX (incidence rate [IR]; [95% CI] per 100 patient-years: 34.62 [14.41–83.17] for postpubertal-onset and 24.24 [9.10–64.60] for prepubertal-onset patients). MG exacerbations were most frequent during the first year of follow-up in both subgroups (34.1% and 30.3%). In postpubertal-onset patients, exacerbation was highest during treatment with maintenance Ig/PLEX and nonsteroid immunosuppressant therapy ([NSIST], mostly polytherapy) (IR [95% CI] 105.81 [68.99–162.29] and 91.22 [65.80–126.47]). For prepubertal-onset patients, exacerbation was most frequent during NSIST (polytherapy) and biologic treatment (IR [95% CI] 140.44 [115.45–170.85] and 142.95 [46.10–443.23]). JMG-related hospitalizations occurred in 36.0% and 30.0% of postpubertal-onset and prepubertal-onset patients, in the first year of follow-up.

Discussion

Patients with JMG escalated rapidly through the treatment hierarchy. Postpubertal-onset patients escalated more quickly to later-line treatments than prepubertal-onset patients. However, some patients continued to experience high HCRU, highlighting the need for new JMG treatments to provide rapid disease control. A limitation is that treatment escalation reasons were not evaluated.

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Glossary

AChEI = acetylcholinesterase inhibitor; **CCAE** = Commercial Claims and Encounters Database; **ED** = emergency department; **HCRU** = health care resource utilization; **ICD** = International Classification of Diseases; **ICU** = intensive care unit; **IR** = incidence rate; **IVIg** = IV immunoglobulin; **JMD** = juvenile myasthenia gravis; **KM** = Kaplan-Meier; **MDCD** = Multi-State Medicaid Database; **NSIST** = nonsteroid immunosuppressant therapy; **PLEX** = plasma exchange; **PY** = patient-year.

Introduction

Juvenile myasthenia gravis (JMG), defined as MG in patients younger than 18 years, is a rare disorder (much rarer than MG in adults) with incidence rates of 0.3–8.9 people per million (as opposed to 100–350 people per million for MG in adults).[1,2] JMG can be purely ocular or generalized.[1] Postpubertal-onset JMG is similar to adult MG regarding the proportion of individuals with generalized onset and rates of remission.[1] However, children with prepubertal onset are more likely to present with purely ocular JMG, as well as higher rates of both spontaneous remission and achievement of complete stable remission, than postpubertal-onset and adult patients.[1,3]

Most conventional treatments used for adult MG are not approved for use in JMG and are prescribed off-label based on adult guidelines and expert opinion.[3-5] Treatment approaches likely differ from physician to physician, and there is a lack of published consensus guidelines for treating JMG. While no international guidelines exist for the treatment of JMG, a European consensus article was published in 2020, which concluded that the treatment goal for JMG should be minimal disease manifestations.[3] For generalized JMG, the European consensus panel recommends pyridostigmine as first-line treatment, followed by initiation of a low dose of oral prednisolone (corticosteroid [CS]) if there is no improvement with pyridostigmine.[3] Numerous adverse effects are associated with CS treatment including hypertension, diabetes and osteoporosis, mood and behavioral disturbance, weight gain, and, of particular importance for treatment of children, growth restriction.[1] Steroid-sparing therapies are, therefore, important for children with JMG.[1,3] Azathioprine is recommended as a first-line steroid-sparing immunosuppressive therapy, and IV immunoglobulin (IVIg) and plasma exchange (PLEX) are generally recommended for acute exacerbations.[3] For refractory JMG, rituximab and maintenance IVIg/PLEX are recommended; rituximab is also used for anti–muscle-specific tyrosine kinase antibody-positive JMG, which is described as a more severe form of disease than anti-acetylcholine receptor antibody-positive JMG, with frequent facial and bulbar muscle weakness involvement.[3,6] In addition, thymectomy is recommended on suspicion of thymoma, although thymoma is rare in patients with JMG,[7] and in nonthymomatous patients, early use of thymectomy should be considered if symptoms are not adequately controlled.[3]

We conducted a longitudinal study using secondary data analysis from claims databases to describe the treatment patterns and disease burden among patients with newly diagnosed JMG in the United States and to explore differences in these variables between prepubertal-onset and postpubertal-onset patients. These findings, reported here, will provide important insights into the current treatment patterns and burden of disease in patients with JMG.

Methods

Study Design and Data Source

This was a longitudinal cohort study of patients with newly diagnosed JMG between January 1, 2008, and December 31, 2021. Two large US insurance claims databases were analyzed to identify newly diagnosed patients with JMG: Merative™ MarketScan® Commercial Claims and Encounters Database (CCAE) and Multi-State Medicaid Database (MDCD). CCAE is a commercial health care claims database that includes claims from employees and their dependents, representing all US census regions, covering several million people.[8] MDCD includes patients covered by Medicaid programs in multiple geographically dispersed states, containing the pooled health care experience of Medicaid enrollees, covered under fee-for-service and managed care plans, encompassing more than 47 million people from multiple states.[8]

Patients with newly diagnosed JMG were identified using the International Classification of Diseases (ICD), Ninth and Tenth Revision (ICD-9 and ICD-10) codes for MG (ICD-9 358.0 including 358.00 and 358.01 and ICD-10 G70.0 including G70.00 and G70.01). These codes do not include neonatal MG or congenital and developmental myasthenia. Two or more diagnosis codes with at least a 3-month gap were required. An index date was assigned based on either a patient's first JMG diagnosis or their first treatment with acetylcholinesterase inhibitors (AChEIs), IV or subcutaneous immunoglobulin (Ig), or PLEX therapy (whichever occurred first). Patients were followed from the index date until the age of 18 years, the discontinuation of medical insurance and pharmacy benefits enrollment, or the study end date (December 31, 2021), whichever occurred first in the database coverage period. To best protect patients' privacy, the databases used for the analysis of this study were selected to only contain information on the year of birth but not the specific day or month. December 31 was, therefore, assigned as the date of birth of all participants to estimate age at any time point.

Study Population

The study population consisted of patients who were aged younger than 18 years on the study start date, with at least 2 MG diagnosis codes, as described above, at least 3 months apart. To ensure that patients were tracked from the very beginning of diagnosis or treatment, eligible patients needed to have at least 180 days of continuous insurance coverage before the index date (waived for participants aged 1 year or younger at the index date), although a ≤60-day gap in insurance enrollment was allowed. Patients were divided into 2 age-at-onset subgroups: those with prepubertal-onset JMG (<12 years of age at index) and those with postpubertal-onset JMG (12–17 years of age at index).

Study Outcomes

The primary outcome was JMG-related treatment patterns during follow-up. Hierarchical treatment cohorts were defined based on the best current understanding of treatment regimens for patients with JMG. Cohorts included time before any treatment (Cohort 0), first AChEI (Cohort 1), first CS (Cohort 2), first maintenance Ig/PLEX (Cohort 3), first nonsteroid immunosuppressant therapy (NSIST) (Cohort 4), and first biologic (monoclonal antibodies rituximab and eculizumab—the only biologics available during the study period; Cohort 5). Time spent in each cohort was identified. A patient could only be in 1 treatment cohort at any given time point during the follow-up and followed a one-way transition from lower to higher treatment cohorts. When patients were in treatment cohorts 2–5, they could have any of the treatments in previous cohorts as background therapy. Patients could also skip treatment cohorts. Secondary outcomes to assess disease burden during follow-up included myasthenic exacerbation, myasthenic crisis, thymectomy, and acute use of IVIg or PLEX. Acute use of IVIg or PLEX was defined as one or more administrations occurring within 7 days. By contrast, maintenance use was defined as any administration after the initial IVIg or PLEX treatment, which occurred more than 7 days but no more than 45 days later. IVIg and PLEX use was evaluated independently. Health care resource utilization (HCRU), including hospitalizations, emergency department (ED) visits, intensive care unit (ICU) admissions, and specialist visits, with a JMG code in any position of diagnosis was also evaluated. A specialist visit was defined as any non-GP visit excluding ED and ICU visits (using MarketScan standard provider codes 100–585 but excluding codes 200, 202, 204, 240, 245, and 400). Exacerbation of JMG was defined as the acute use of IVIg or PLEX or inpatient hospitalization with JMG diagnosis reported during the same hospitalization. Myasthenic crisis was defined as the occurrence of all three of the following criteria within one 7-day window: MG diagnosis (not necessarily during inpatient stays); acute use of IVIg and/or PLEX; and respiratory failure or mechanical ventilation in an inpatient setting.

Analysis

Statistical analysis and generation of tables, figures, patient data listings, and statistical output were performed using SAS version 9.4. Continuous variables were summarized using descriptive statistics with mean, SD, median, interquartile range, minimum, and maximum, unless otherwise specified. All categorical variables were presented using frequency counts and percentages. Time from index date to the first use of CS or to thymectomy was plotted on a Kaplan-Meier (KM) survival curve for postpubertal-onset and prepubertal-onset subgroups. Patients were censored when they reached 18 years of age, discontinued medical insurance enrollment, or reached the study end date (December 31, 2021), whichever occurred first. Where used, nominal p values were generated using log-rank tests to compare the postpubertal-onset and prepubertal-onset subgroups. No imputation was applied to missing data.

Standard Protocol Approvals, Registrations, and Patient Consents

The databases are Health Insurance Portability and Accountability Act compliant, and all patient data were deidentified before delivery to the study team.

Data Availability

Data from noninterventional studies are outside UCB's data-sharing policy and are unavailable for sharing.

Results

Patient Demographics

Between January 1, 2008, and December 31, 2021, 630 patients with newly diagnosed JMG were identified (Table 1). One patient was followed for <3 months and was, therefore, excluded from these analyses. The mean age at JMG diagnosis was 9.07 years; 42.4% (267/630) of patients had postpubertal-onset JMG, and 57.6% (363/630) had prepubertal onset. In the overall population, 64.1% were female; 69.3% and 60.3% were female in the postpubertal-onset and prepubertal-onset groups, respectively (Table 1).

Treatment Patterns

The median (range) follow-up time for the postpubertal-onset and prepubertal-onset groups was 1.9 (0–6) years and 3.4 (0–13) years, respectively. The median (range) follow-up time for the overall population was 2.4 (0–13) years. Movement of patients through treatment cohorts is shown in Figure 1. Of the postpubertal-onset patients, 76.3% started treatment within 3 months of diagnosis, compared with 66.9% of prepubertal-onset patients.

Postpubertal-onset patients were prescribed CS (Cohort 2) and maintenance Ig/PLEX (Cohort 3) earlier than the patients in the prepubertal-onset group (Figure 2). Among the patients who were prescribed a biologic (Cohort 5), 77.8% (7/9) in the postpubertal-onset group and 92.3% (12/13) in the prepubertal-onset group received rituximab and 22.2% (2/9) and 7.7% (1/13) received eculizumab, respectively. No patients were prescribed a second biologic. The NSIST treatment cohort (Cohort 4) had the lowest use of monotherapy (12.5% of patients in postpubertal-onset and none in prepubertal-onset groups) and the greatest use of polytherapy, with 3 or more classes of treatment (65.0% in postpubertal-onset and 76.7% in prepubertal-onset groups) (eFigure 1).

Table 1 Baseline Characteristics in the Overall Population and by Age at Onset

	Postpubertal onset (aged 12–17 y)	Prepubertal onset (aged younger than 12 y)	Overall population
Patients, n	267[a]	363[a]	630
Sex, female, n (%)	185 (69.3)	219 (60.3)	404 (64.1)
Age at JMG diagnosis, y			
Median (range)	15 (12–17)	5 (0–11)	10 (0–17)
IQR	3	6	10
Mean (SD)	14.72 (1.59)	4.91 (3.77)	9.07 (5.73)
Health care insurance, n			
CCAE	167	156	323
MDCD	100	207	307
Comorbidities, n (%)			
Infection	45 (16.9)	80 (22.0)	125 (19.8)
Depression	26 (9.7)	10 (2.8)	36 (5.7)
Anxiety	48 (18.0)	45 (12.4)	93 (14.8)

Abbreviations: CCAE = Commercial Claims and Encounters Database; IQR = interquartile range; JMG = juvenile myasthenia gravis; MDCD = Multi-State Medicaid Database.
Comorbidities include only those that occurred in more than 5% of patients among the overall population.
[a] Postpubertal-onset and prepubertal-onset patients comprised 42.4% and 57.6%, respectively, of the overall population.

In KM survival analysis, the median (range) time from index date to the first use of any CS was 1.38 (0.03–37.05) months in the postpubertal-onset group and 3.53 (0.03–87.72) months in the prepubertal-onset group (nominal p value = 0.2564, log-rank test).

Thymectomy

In the postpubertal-onset subgroup, the IR of thymectomy was highest in the first year of follow-up (22.33 per 100 patient-years [PY]; 95% CI 16.78–29.73) and then decreased across subsequent years (second year: 3.07 [1.15–8.18]; third year: 1.34 [0.19–9.52]) (eTable 1). Similarly, in the prepubertal-onset subgroup, the IR of thymectomy was highest in the first year of follow-up (9.91 per 100 PY; 95% CI 7.04–13.94) and then decreased across subsequent years (second year: 1.67 [0.63–4.45]; third year: 1.61 [0.52–4.99]) (eTable 1). Thymectomy was more frequent in postpubertal-onset patients than in prepubertal-onset patients across all treatment cohorts (Figure 3). Median (range) time to thymectomy was shorter in the postpubertal-onset group (5.18 [0.43–29.72] months) than in the prepubertal-onset group (7.58 [0.72–100.57] months). Survival analysis using KM estimates also indicated a shorter time to thymectomy for postpubertal-onset than for prepubertal-onset patients (mean [SD] time of 5.98 [5.56] months vs 14.23 [18.56] months; nominal p value = 0.0004, log-rank test; eFigure 2).

Twelve-month KM estimates for the probability of thymectomy were 19.3% and 9.5% for the postpubertal-onset and prepubertal-onset patients, respectively, while 24-month KM estimates were 21.6% and 11.0%, respectively.

Myasthenic Exacerbations and Crises

JMG-related exacerbations occurred in the highest proportion of patients in the first year of follow-up in both subgroups (34.1% and 30.3% in postpubertal-onset and prepubertal-onset groups, respectively) (eTable 1). During the second year of follow-up, JMG-related exacerbations occurred in 15.6% and 10.4% of patients, respectively (eTable 1).

In the postpubertal-onset group, JMG-related exacerbations were most frequent in patients in the maintenance Ig/PLEX cohort (Cohort 3) and the NSIST cohort (Cohort 4) (Figure 4), while for prepubertal-onset patients, exacerbations were most frequent in patients in the NSIST treatment cohort (Cohort 4) and the biologics cohort (Cohort 5) (Figure 4). Myasthenic crises and rescue treatment with IVIg and PLEX are also presented in Figures 4 and 5.

HCRU

JMG-related hospitalizations, ED visits, and ICU admissions were all highest in the first year of follow-up, occurring in 36.0%, 26.6%, and 17.6% of patients in the postpubertal-onset subgroup, respectively (eTable 1). In the prepubertal-onset subgroup, these events occurred in 30.0%, 27.8%, and 15.2% of patients in the first year of follow-up, respectively. During the second year of follow-up, JMG-related exacerbations, ED visits, and ICU admissions occurred in 11.1%, 14.1%, and 5.5% in the postpubertal-onset subgroup and 9.1%, 13.6%, and 4.5% of patients in the prepubertal-onset subgroup, respectively (eTable 1).

Mean length of JMG-related hospital stay was highest in patients in the maintenance Ig/PLEX cohort (Cohort 3) and the NSIST cohort (Cohort 4) in both the postpubertal-onset and the prepubertal-onset groups (Table 2).

Although, in patients in the maintenance Ig/PLEX cohort, the high rate of JMG-related admission to ICU was driven by the prepubertal-onset group, the rate of JMG-related ED visits in patients in the maintenance Ig/PLEX cohort was similar between the 2 groups (Table 2).

In the postpubertal-onset group, JMG-related specialist visits were most frequent in patients in the biologics cohort (Cohort 5) while, in the prepubertal-onset group, the peak IR per patient-years (PY) of JMG-related specialist visits was in patients in the maintenance Ig/PLEX cohort (Cohort 3) (Table 2). HCRU for the overall population is provided in eTable 2.

Discussion

Owing to the rarity of JMG, little knowledge exists on current treatment patterns and HCRU for patients with JMG.

Figure 1 Treatment Escalation Patterns in (A) Postpubertal-Onset Patients, (B) Prepubertal-Onset Patients, and (C) the Overall Population

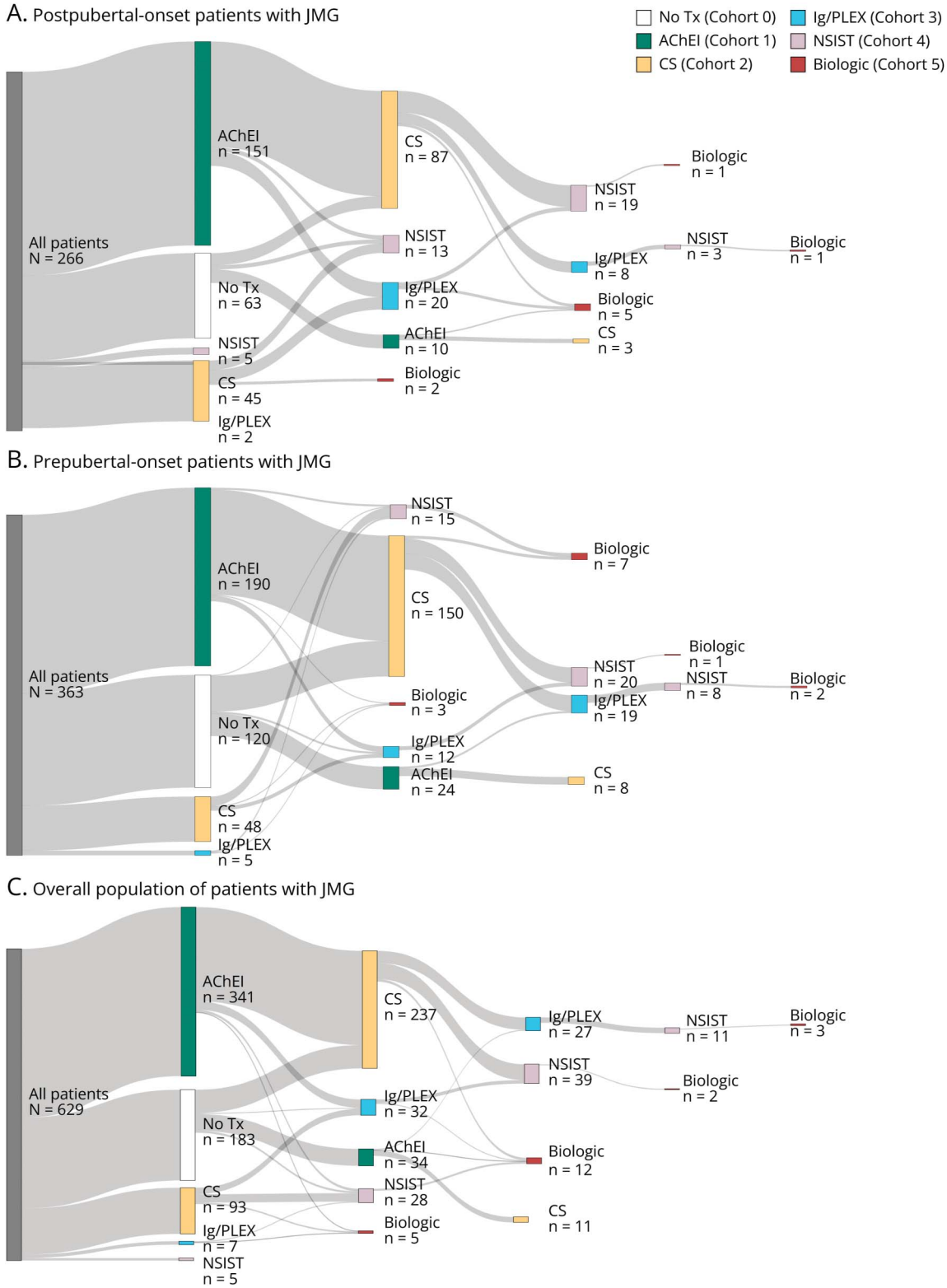
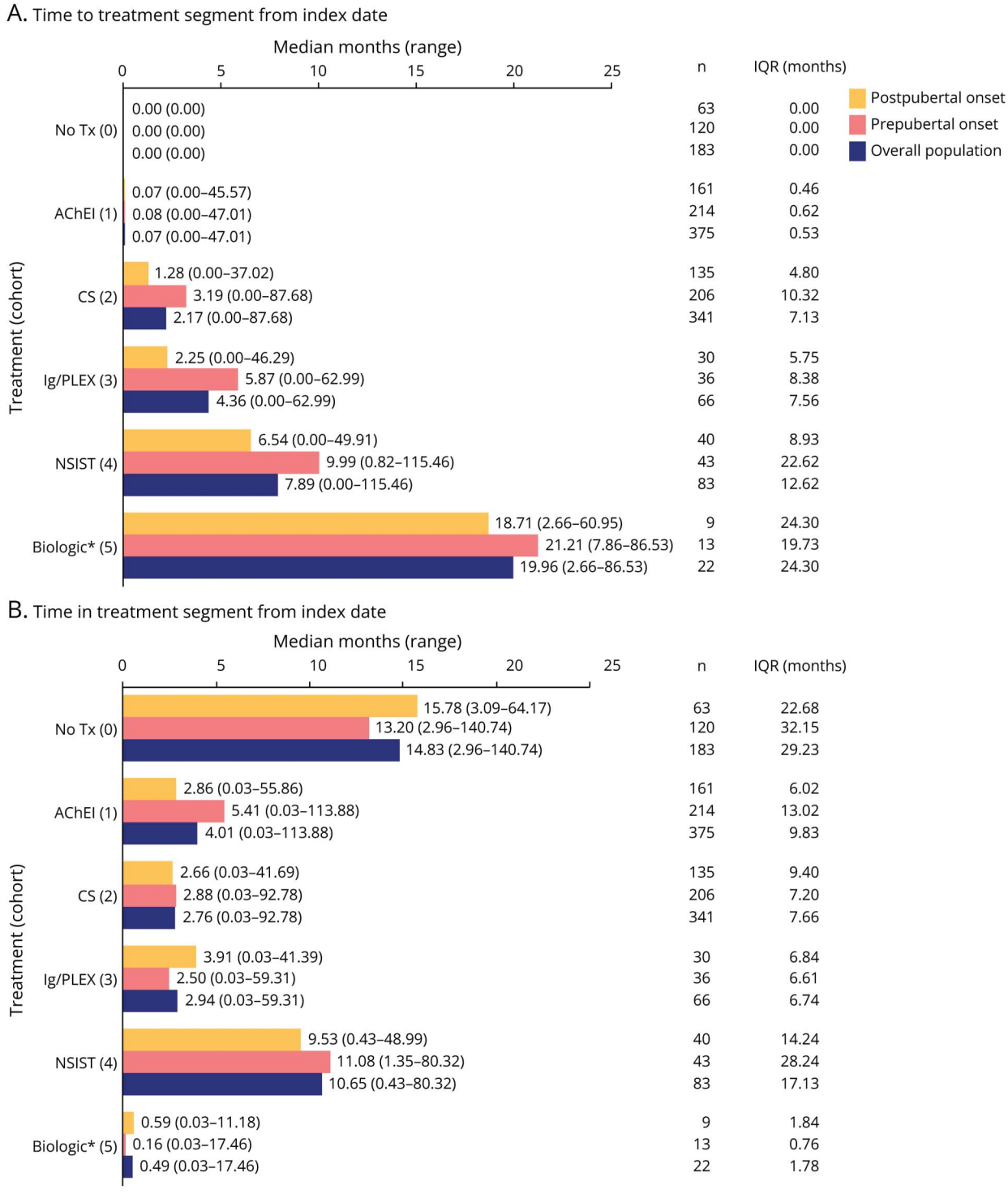


Figure shows the movement of patients between treatments at any time during the period under analysis. To be counted in the "no treatment" cohort, patients must have remained without treatment for the whole of the first 3 months. Of the 630 patients initially identified, 1 did not receive any treatment but was followed for less than 3 months and so did not qualify for the "no treatment" cohort. This patient was, therefore, excluded, and all analyses involving treatment cohorts were based on 629 patients. AChEI = acetylcholinesterase inhibitor; CS = corticosteroid; Ig = immunoglobulin; JMG = juvenile myasthenia gravis; NSIST = nonsteroid immunosuppressant therapy; PLEX = plasma exchange; Tx = treatment.

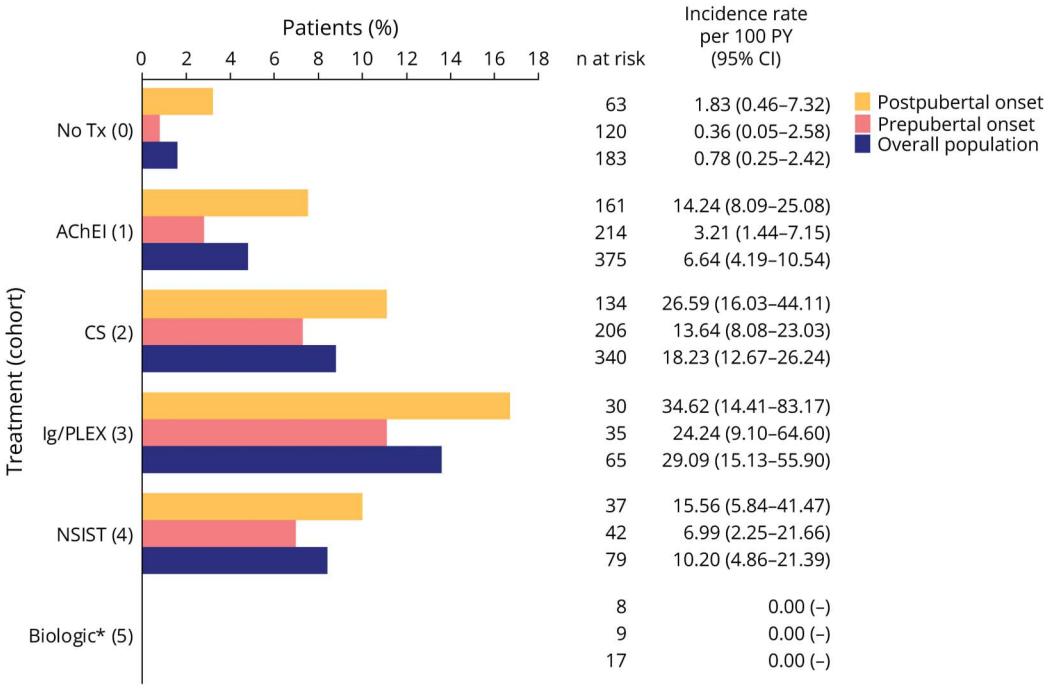
Figure 2 (A) Time to Treatment Segment and (B) Time in Each Treatment Cohort From Index Date by Age at Onset of JMG and in the Overall Population



Of the 630 patients initially identified, 1 patient was followed for <3 months and was, therefore, excluded from these analyses. *Rituximab or eculizumab. AChEI = acetylcholinesterase inhibitor; CS = corticosteroid; Ig = immunoglobulin; IQR = interquartile range; JMG = juvenile myasthenia gravis; NSIST = nonsteroid immunosuppressant therapy; PLEX = plasma exchange; Tx = treatment.

Consensus guidance is limited and reliant on adult guidelines, which may not be appropriate for all patients with JMG. This observational, secondary data analysis of health care claims data from more than 600 patients with JMG in the United States highlights the high rates of exacerbations and rescue therapy use in this population, despite treatment, suggesting that current treatments may not provide adequate disease control for all pediatric patients. This aligns

Figure 3 Incidence of Thymectomy in Each Treatment Cohort by Age at Onset of JMG and in the Overall Population



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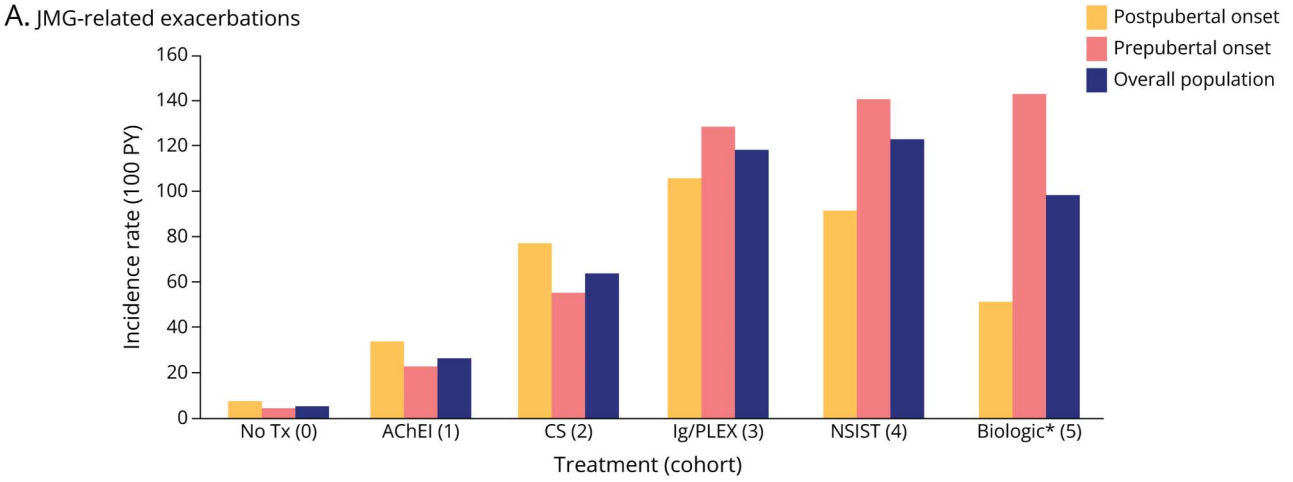
with a recent US claims study of treatment patterns in adults with MG that found that some patients have uncontrolled MG despite chronic treatments, with around half experiencing MG exacerbations and requiring hospitalization.[9] Our findings highlight important differences in treatment patterns and HCRU in postpubertal-onset vs prepubertal-onset patients with JMG, which could reflect individualized approaches to JMG management that clinicians may take based on age at diagnosis.

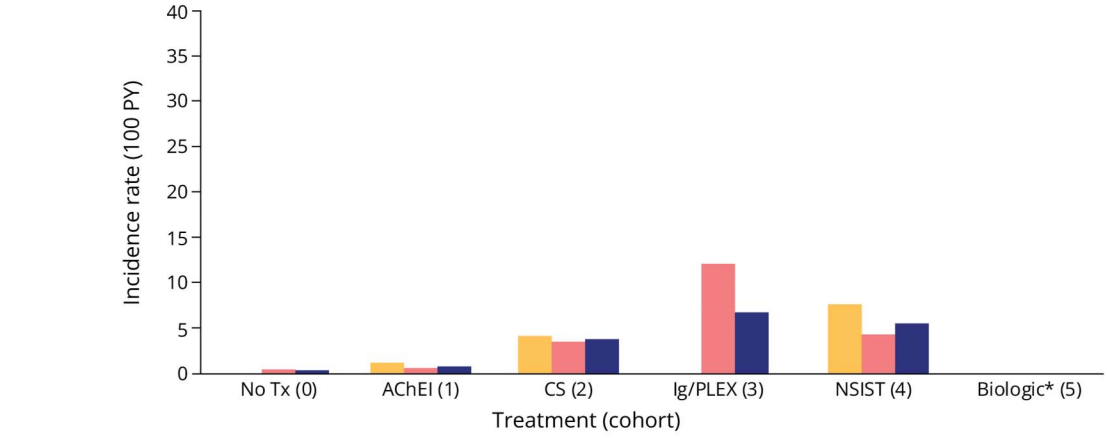
In our study, we found that treatment of patients with JMG was usually initiated within 3 months of diagnosis. Most physicians start JMG treatment promptly in pediatric patients because, with a developing nervous system, it is important to avoid fixed, unrecoverable deficits. This is particularly important in ocular MG—which is more common in prepubertal-onset patients than in postpubertal-onset patients—to avoid neuromuscular junction damage becoming irreversible.[10-13] However, per our study, up to 1 in 3 children did not have JMG-related treatment initiated within 3 months. Reasons for this may include inexperience in prescribing JMG treatment in young children or reluctance on the part of physicians or caregivers to start treatment. For example, chronic CS use is associated with several adverse effects, such as growth inhibition, and consequently, corticosteroids are often used with caution in pediatric patients.[5] In addition, diagnosis of JMG in prepubertal-onset patients can be challenging and time-consuming. For example, the proportion of seronegative patients is higher than in the postpubertal-onset group, making it more difficult to differentiate JMG from congenital myasthenic syndromes, resulting in diagnostic delay and a subsequent delay in starting treatment.[14] Any uncertainty while a firm diagnosis is reached may explain a more cautious, steroid-sparing approach in patients who are still growing.

Despite having a large variance, our data show that movement through treatment cohorts was generally rapid, with postpubertal-onset patients moving more quickly through the treatment hierarchy than prepubertal-onset patients. The faster escalation of postpubertal-onset patients may be due to several factors. In general, prepubertal-onset patients are more likely to have milder disease and a higher rate of spontaneous remission.[1,3] Furthermore, a higher proportion of patients with prepubertal-onset JMG have ocular MG than those with postpubertal-onset JMG.[1,15-17] In addition, symptoms in younger patients are often missed by caregivers, and as a result, disease in these patients may progress further before health care advice is sought, leading to delays in treatment escalation. Although data were not available to confirm the baseline disease severity of the patients in our study, a recent study in China with 859 patients with JMG found milder disease in the prepubertal-onset group than in the postpubertal-onset group.[15] It is important to note that treatment cohorts and outcomes are not independent and a patient in a higher treatment cohort, who is at an advanced stage in the treatment pathway, is likely to have more severe

Figure 4 (A) JMG-Related Exacerbation and (B) Myasthenic Crises in Each Treatment Cohort by Age at Onset of JMG and in the Overall Population



n	63 120 183	161 214 375	135 206 341	30 36 66	40 43 83	9 13 22
Postpubertal onset, IR, 100 PY (95% CI)	7.27 (3.64–14.54)	33.84 (23.80–48.12)	77.05 (59.44–99.89)	105.81 (68.99–162.29)	91.22 (65.80–126.47)	50.98 (7.18–361.89)
Prepubertal onset, IR, 100 PY (95% CI)	3.99 (2.21–7.20)	22.74 (16.92–30.56)	55.27 (43.26–70.61)	128.38 (90.79–181.54)	140.44 (115.45–170.85)	142.95 (46.10–443.23)
Overall population, IR, 100 PY (95% CI)	4.92 (3.14–7.72)	26.31 (20.98–32.99)	63.76 (53.35–76.20)	118.38 (90.44–154.95)	122.89 (103.88–145.38)	98.52 (36.97–262.49)



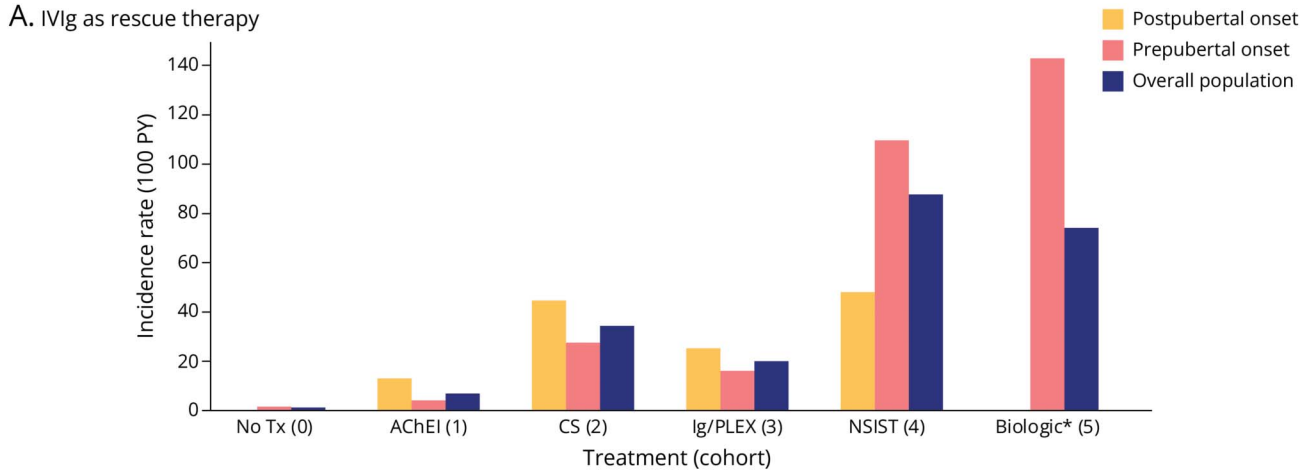
Postpubertal onset, IR, 100 PY (95% CI)	0.00 (–)	1.09 (0.15–7.75)	4.06 (1.31–12.57)	0.00 (–)	7.60 (2.45–23.57)	0.00 (–)
Prepubertal onset, IR, 100 PY (95% CI)	0.36 (0.05–2.57)	0.52 (0.07–3.67)	3.45 (1.30–9.20)	12.04 (3.88–37.32)	4.21 (1.36–13.06)	0.00 (–)
Overall population, IR, 100 PY (95% CI)	0.26 (0.04–1.84)	0.70 (0.18–2.80)	3.69 (1.76–7.74)	6.70 (2.16–20.78)	5.42 (2.44–12.07)	0.00 (–)

Of the 630 patients initially identified, 1 patient was followed for <3 months and was, therefore, excluded from these analyses. *Rituximab or eculizumab. AChEI = acetylcholinesterase inhibitor; CS = corticosteroid; Ig = immunoglobulin; IR = incidence rate; JMG = juvenile myasthenia gravis; NSIST = nonsteroid immunosuppressant therapy; PLEX = plasma exchange; PY = patient-year; Tx = treatment.

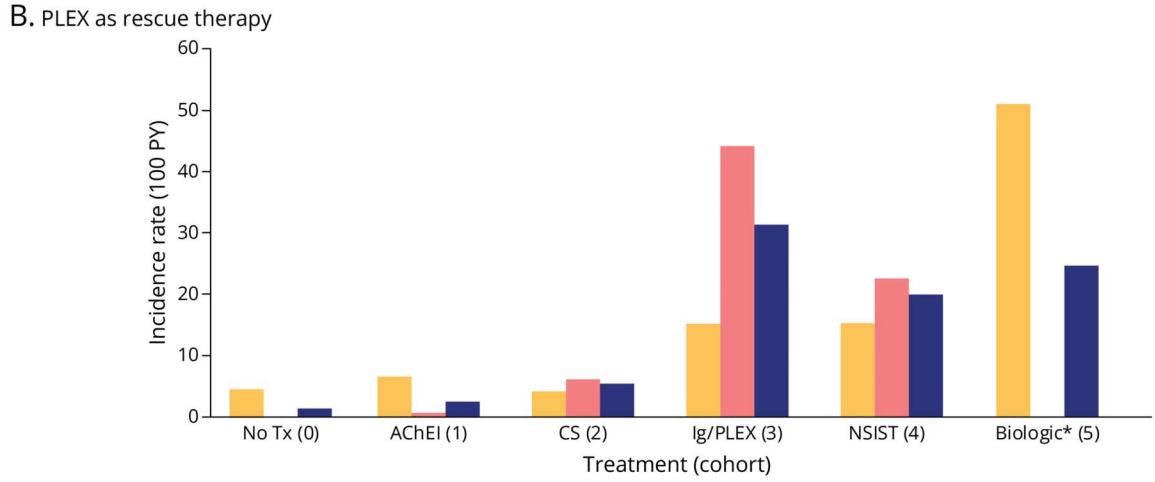
MG and hence higher rates of exacerbation and HCRU. In our study, MG exacerbation rates were higher in postpubertal-onset patients vs prepubertal-onset patients in every follow-up year after JMG diagnosis, which indicates that the former may have had more severe disease on average at baseline than the latter. This emphasizes the importance of assessing patients with prepubertal-onset and postpubertal-onset JMG separately.

While high HCRU burden has also been reported for some adults with generalized myasthenia gravis,[9] the high HCRU observed in a proportion of patients in this study has additional implications for both the child and their family. Considerable time away from school will have both educational and social consequences for a child. Accompanying a child to specialist appointments or during hospital stays may result in burden on caregivers and affect the ability to work for an adult

Figure 5 (A) IVIg and (B) PLEX Use as Rescue Therapy in Each Treatment Cohort by Age at Onset of JMG and in the Overall Population



n	63 120 183	161 214 375	135 206 341	30 36 66	40 43 83	9 13 22
Postpubertal onset, IR, 100 PY (95% CI)	0.00 (–)	13.10 (7.44–23.06)	44.61 (31.71–62.75)	25.19 (10.49–60.53)	48.15 (30.71–75.48)	0.00 (–)
Prepubertal onset, IR, 100 PY (95% CI)	1.45 (0.54–3.86)	4.13 (2.07–8.27)	27.63 (19.54–39.08)	16.05 (6.02–42.76)	109.55 (87.74–136.77)	142.95 (46.10–443.23)
Overall population, IR, 100 PY (95% CI)	1.04 (0.39–2.76)	7.02 (4.53–10.87)	34.25 (26.86–43.68)	20.10 (10.46–38.63)	87.65 (71.83–106.95)	73.89 (23.83–229.09)



Postpubertal onset, IR, 100 PY (95% CI)	4.54 (1.89–10.92)	6.55 (2.94–14.58)	4.06 (1.31–12.57)	15.12 (4.88–46.87)	15.20 (6.83–33.84)	50.98 (7.18–361.89)
Prepubertal onset, IR, 100 PY (95% CI)	0.00 (–)	0.52 (0.07–3.67)	6.05 (2.88–12.68)	44.13 (24.44–79.69)	22.47 (13.77–36.68)	0.00 (–)
Overall population, IR, 100 PY (95% CI)	1.30 (0.54–3.11)	2.46 (1.17–5.15)	5.27 (2.84–9.79)	31.27 (18.52–52.80)	19.88 (13.09–30.19)	24.63 (3.47–174.84)

Of the 630 patients initially identified, 1 patient was followed for <3 months and was, therefore, excluded from these analyses. *Rituximab or eculizumab. AChEI = acetylcholinesterase inhibitor; CS = corticosteroid; Ig = immunoglobulin; IR = incidence rate; IVIg = IV immunoglobulin; JMG = juvenile myasthenia gravis; NSIST = nonsteroid immunosuppressant therapy; PLEX = plasma exchange; PY = patient-year; Tx = treatment.

carer, resulting in loss of earnings, as well as affecting their mental health and the ability to care for siblings.[18,19] Our findings suggest that prescribing targeted therapies earlier in the treatment pathway could help to reduce disease burden and HCRU for patients with JMG. Development of new therapies that are more easily administered than the existing therapies and access to multidisciplinary teams, including physiotherapists, ophthalmologists, and psychologists if needed, may improve quality of life for children with JMG and may reduce the burden of disease for both patients and their families.

In this study, the rates of thymectomy observed were generally lower than expected, with an IR of 14.72 per 100 PY in the first year of follow-up. There was a lower rate of, and longer time to, thymectomy in prepubertal-onset patients than in

Table 2 JMG-Related Health Care Resource Utilization by Treatment and by Age at Onset

	Treatment (cohort)					
	No Tx (0)	AChEI (1)	CS (2)	Ig/PLEX (3)	NSIST (4)	Biologic[a] (5)
Postpubertal onset, n	63	161	135	30	40	9
Hospitalization						
No. of events	6	33	51	20	24	0
IR, 100 PY (95% CI)	5.45 (2.45–12.14)	36.02 (25.61–50.67)	68.94 (52.40–90.71)	100.77 (65.01–156.20)	60.82 (40.76–90.73)	0.00 (–)
Mean LOS, d	0.76	1.41	2.09	3.30	3.68	0.00
ICU visits						
No. of events	3	17	18	4	12	1
IR, 100 PY (95% CI)	2.73 (0.88–8.45)	18.56 (11.54–29.85)	24.33 (15.33–38.62)	20.15 (7.56–53.70)	30.41 (17.27–53.54)	50.98 (7.18–361.89)
ED visits						
No. of events	15	26	40	23	41	1
IR, 100 PY (95% CI)	13.63 (8.22–22.61)	28.38 (19.32–41.68)	54.07 (39.66–73.72)	115.89 (77.01–174.39)	103.89 (76.50–141.10)	50.98 (7.18–361.89)
Specialist visits						
No. of events	87	376	412	133	309	23
IR, 100 PY (95% CI)	79.06 (64.07–97.54)	410.42 (370.96–454.07)	556.94 (505.68–613.40)	670.14 (565.40–794.28)	783.01 (700.40–875.37)	1,172.49 (779.15–1764.39)
Prepubertal onset, n	120	214	206	36	43	13
Hospitalization						
No. of events	9	45	53	31	19	0
IR, 100 PY (95% CI)	3.26 (1.70–6.27)	23.26 (17.36–31.15)	45.77 (34.97–59.91)	124.37 (87.46–176.84)	26.68 (17.02–41.83)	0.00 (–)
Mean LOS, d	1.19	1.53	1.84	4.50	4.00	0.00
ICU visits						
No. of events	6	21	30	25	11	0
IR, 100 PY (95% CI)	2.18 (0.98–4.84)	10.85 (7.08–16.65)	25.91 (18.11–37.05)	100.30 (67.77–148.43)	15.45 (8.56–27.90)	0.00 (–)
ED visits						
No. of events	25	80	81	29	46	0
IR, 100 PY (95% CI)	9.06 (6.12–13.41)	41.35 (33.21–51.48)	69.95 (56.26–86.97)	116.34 (80.85–167.42)	64.60 (48.39–86.25)	0.00 (–)
Specialist visits						
No. of events	150	435	600	219	562	12
IR, 100 PY (95% CI)	54.38 (46.34–63.82)	224.82 (204.66–246.97)	518.15 (478.30–561.31)	878.60 (769.61–1,003.02)	789.30 (726.66–857.32)	571.80 (324.73–1,006.85)

Abbreviations: AChEI = acetylcholinesterase inhibitor; CS = corticosteroid; ED = emergency department; ICU = intensive care unit; Ig = immunoglobulin; IR = incidence rate; JMG = juvenile myasthenia gravis; LOS = length of stay; NSIST = nonsteroid immunosuppressant therapy; PLEX = plasma exchange; PY = patient-year; Tx = treatment.
Of the 630 patients initially identified, 1 patient was followed for <3 mo and was, therefore, excluded from these analyses.
[a] Rituximab or eculizumab.

post-pubertal-onset patients. Current guidance suggests that early use of thymectomy in nonthymomatous patients with anti-AChR autoantibody-positive JMG should be considered if symptoms are not adequately controlled.[3] A systematic review of 488 patients with JMG who underwent thymectomy showed the procedure to be well tolerated, and 77% had

improved symptoms after surgery.[20] Several studies on the use of thymectomy in JMG demonstrated good disease control, with some studies highlighting a subsequent reduction in steroid use.[21-27] However, the role of thymectomy in patients with milder JMG is uncertain because of the high rate of spontaneous remission, particularly in ocular-only patients, and the potential effect on immunologic maturation in very young children.[1,2] In addition, a multidisciplinary team needs to include a thoracic surgeon to perform thymectomy. All these factors may explain the low rates of thymectomy observed in this study's overall population and especially in the prepubertal-onset group.

There are few studies on treatments of JMG, and most are not controlled, are open-label, and have small patient numbers because of the rarity of JMG. A study of 27 children showed that PLEX and IVIg had good response rates as maintenance therapies for JMG, with PLEX having a more consistent response rate.[28] However, both PLEX and IVIg are associated with safety concerns; there are also issues with venous access for PLEX,[29] and dependence on donor supply for IVIg. In a retrospective study of 74 patients with JMG in France, early use of rituximab improved JMG-related outcomes and facilitated corticosteroid sparing.[30] Similarly, another study of rituximab with 5 patients showed that most patients experienced fewer JMG-related hospital admissions.[31] There are only a few treatments approved for JMG, and hence, specific JMG treatment guidelines are lacking, with no internationally accepted standards of care. Eculizumab, a targeted complement component 5 inhibitor, has recently been approved for use in the EU and Japan for the treatment of children and adolescents with refractory generalized MG who are anti-AChR antibody-positive.[32-34] A European Neuromuscular Centre workshop group published guidance on the management of JMG in 2020, but the international guidelines, as with the national treatment guidelines for MG in the United Kingdom and Belgium, provide no specific guidance for JMG.[3,35-37] A recently published guideline for MG in Germany recommends that patients with JMG should be treated in the same way as patients with adult MG, and that the possibility of occurrence of spontaneous remission should be considered in patients with prepubertal-onset JMG.[38] Current treatment practices in JMG are thus based on guidelines for adult patients and expert opinion derived from individual clinical experience,[1] but treatments used widely in adults with MG may not be optimal for all patients with JMG because different age at onset and related developmental stages, and potential for differences in tolerability of treatments, need to be taken into consideration. Furthermore, with the emergence and approval of novel treatments for MG that are not approved for use in the pediatric population, the guidelines for adult MG are evolving rapidly and, therefore, may not be applicable to JMG. This highlights the importance of expanding clinical trials to gain rapid pediatric approvals and developing widespread consensus statements on treating JMG. The findings presented here, particularly those that highlight age-dependent differences in treatment outcomes, could be used to inform the development of JMG-specific guidelines.

However, there are some limitations to our study. First, the same ICD code is used for ocular and generalized MG, and therefore, our analysis did not permit any distinction between the 2. The patients with anti-AChR autoantibody-positive, anti-MuSK autoantibody-positive, and seronegative JMG could not be differentiated. Further studies may be warranted to assess any association between HCRU and antibody status in the JMG population. Reasons for treatment escalation, whether for lack of efficacy or due to adverse effects, were not available. Because this is a claims database analysis, the time to treatment could only be calculated from diagnosis and not from symptom onset. Acute use and maintenance use of IVIg and PLEX were not differentiated by distinct codes in the claims databases, and use of our protocol definitions may have resulted in some misclassifications. The number of exacerbations may have been overestimated because it was not possible to verify whether each hospitalization with a JMG diagnosis was due to exacerbation. In addition, patient numbers were very low in some treatment cohorts, especially the biologics cohort, because neither eculizumab nor rituximab was licensed for use in the pediatric population at the time of the study. Furthermore, our study only reflects data collected in the United States and may have limited generalizability to other countries. The treatments analyzed here reflect those in use at the time of the study, and findings should be updated as new treatments are granted licenses for use in JMG and become established therapies in clinical practice.

In conclusion, JMG carries a high health care burden, with high rates of hospitalization, ICU care, and specialist visits. The differences observed in the treatment patterns between patients with postpubertal-onset and prepubertal-onset JMG highlight that an individualized approach should be used for these subgroups. At a time when this population should be able to fully participate in the education system and socialize, the impact of inadequate disease control during childhood has both short-term and long-term implications for their physical health and mental well-being. Despite current treatment options, there are still patients with JMG experiencing a high burden of disease. Clinical trials in the pediatric population that may lead to new treatments that can provide rapid and adequate disease control in JMG are needed to reduce the burden of disease to patients and their caregivers and to decrease the costs associated with high HCRU.

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