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ORIGINAL ARTICLE

Treatment of juvenile myasthenia gravis with tacrolimus: A cohort study

Guoli Wang[1,2,3] | Miriam Kessi[1] | Xi Huang[1] | Wen Zhang[1,2,3] | Ciliu Zhang[1,2,3] | Fang He[1,2,3] | Jing Peng[1,2,3] | Fei Yin[1,2,3] | Lifen Yang[1,2,3]

[1]Department of Pediatrics, Xiangya Hospital, Central South University, Changsha, China

[2]Hunan Intellectual and Developmental Disabilities Research Center, Changsha, China

[3]Clinical Research Center for Children Neurodevelopmental Disabilities of Hunan Province, Xiangya Hospital, Central South University, Changsha, China

Correspondence
Lifen Yang, Department of Pediatrics, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China.
Email: yanglifen7@126.com

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Abstract

Background: We investigated the proper timing, efficacy and safety of tacrolimus for juvenile myasthenia gravis (JMG).

Methods: We conducted a retrospective cohort study for JMG patients treated with tacrolimus at Xiangya Hospital, Central South University, Changsha, China from 2010 to 2023. The clinical information of patients with a follow-up of more than 1 year was collected. Comparisons of clinical features between groups of patients who achieved therapeutic goal and those who did not achieve therapeutic goal as well as between groups of patients treated with tacrolimus within or after 1 year from JMG onset was carried out.

Results: Forty-three patients were enrolled, of whom 28 achieved therapeutic goal. Tacrolimus reduced glucocorticoids (GC) dosages for the 28 cases and 15 cases discontinued GC completely. Generalized myasthenia gravis (GMG) subtype had an association with a group of patients who achieved therapeutic goal ($p = 0.001$). Median duration from JMG onset to tacrolimus use was 10.50 months for those who achieved therapeutic goal and 36.00 months for those who did not achieve therapeutic goal ($p = 0.010$). The median Myasthenia Gravis Activities of Daily Living (MG-ADL) score improved significantly ($p = 0.003$). The initiation of tacrolimus within 1 year of JMG onset showed an association with achievement of therapeutic goal ($p = 0.026$). GMG subtype showed an association with a group of patients who received tacrolimus within 1 year ($p = <0.001$). Tacrolimus side effects were tolerable.

Conclusion: The provision of tacrolimus within 1 year of JMG onset is effective and safe.

KEYWORDS
efficacy, generalized myasthenia gravis, glucocorticoids, juvenile myasthenia gravis, ocular myasthenia gravis, safety, tacrolimus, timing

INTRODUCTION

Myasthenia gravis (MG) is an autoantibody-mediated disease that affects neuromuscular junctions. The incidence of juvenile myasthenia gravis (JMG) varies according to ethnic group; there is a four times higher incidence rate of JMG in Asia compared with Europe and North America [1]. The prevalence of JMG in children aged below 10 years is 50% for Chinese, 9% for Japanese and 2% for Italian children [1]. Therapies for JMG include several immunosuppressive agents. Corticosteroids are the first-line immunosuppressive

agents used in MG; however, not all patients respond to this treatment alone. Long-term use of corticosteroids has a range of side effects including effects on growth, puberty and bone health [2]. Nonsteroidal immunosuppressants (IS) including azathioprine, tacrolimus, rituximab and mycophenolate mofetil can sometimes be added when patients do not respond sufficiently to corticosteroids alone [2]. An adult, non-randomized study revealed that the addition of tacrolimus to corticosteroids for post-thymectomy patients resulted in a higher proportion of patients achieving complete stable remission within a shorter time compared with patients who received prednisolone alone [3]. Tacrolimus enabled reduction of prednisolone or cessation of steroid treatment, which could diminish the serious side effects related to long-term steroid treatment for post-thymectomy patients [3].

Although several studies have reported on the efficacy and safety of tacrolimus in adult patients, some of which reported on a mixture of adults and children, there are limited studies for pure JMG [4–7]. The proper timing, efficacy and safety of tacrolimus for pure JMG patients are unknown. Therefore, we aimed to investigate the possible proper timing, efficacy and safety of tacrolimus for JMG patients. To the best of our knowledge, this is the first study to investigate the possible proper timing of tacrolimus for a pure JMG population that received corticosteroids and tacrolimus without other IS or thymectomy as in other previous studies. This study provides additional evidence and guidance for clinicians regarding treatment of JMG.

METHODS

This study was conducted retrospectively and was approved by the ethical committee of Xiangya Hospital, Central South University, Changsha, China (approval number 202310892). It was conducted according to the tenets of the Declaration of Helsinki. We reviewed medical records of all patients to collect clinical data before treatment comprising age, sex, disease course, serum autoantibodies status, Myasthenia Gravis Foundation of America (MGFA) classification as well as follow-up data including MGFA post-intervention status (MGFA PIS) [8] and Myasthenia Gravis Activities of Daily Living (MG-ADL) scale whenever possible [9]. The parents/guardians of the participants provided informed written consent. All included patients were diagnosed with JMG before the age of 14 years, from May 2010 to January 2023 at the Department of Pediatrics, Xiangya Hospital, Central South University, Changsha, China. Patients included in this study met the following criteria: (i) diagnosed with JMG before the age of 14 years, (ii) received tacrolimus for more than 3 months; (iii) had a follow-up duration of more than 1 year; (iv) with at least one of the following confirmatory tests: (a) unequivocally positive response to intramuscular injection of a bolus of neostigmine sulfate, (b) positive serum acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) antibodies, and (c) positive repetitive nerve stimulation (RNS) results. Patients without contact information, insufficient baseline data, those who had ever received other maintaining IS (including azathioprine, mycophenolate mofetil and long-term intravenous immunoglobulin), those whose tacrolimus was withdrawn due to adverse events, those who received glucocorticoids (GC, prednisolone) only, patients who were diagnosed with congenital myasthenic syndrome or mitochondrial diseases and those who refused to participate were excluded.

Our patients were diagnosed according to the protocols described in our previous publications [10, 11]. Antibodies were measured using enzyme-linked immunosorbent assay (ELISA) and RNS was performed whenever possible. Symptoms, signs, comorbidities and laboratory tests including complete blood count, liver and renal function tests, muscle enzymes, fasting blood glucose, lipid profile and electrolytes levels were checked regularly to monitor the side effects of the GC and tacrolimus during follow-up. Thymic hyperplasia was evaluated by computed tomography (CT) scan. Treatment was personalized to the individual patient according to the guidelines, clinicians' experience and parents/guardians' wishes. Briefly, all patients received oral pyridostigmine first and GC was added when patients did not improve or worsened for a few days to months. GC dosages were adjusted according to the individual's disease condition. Patients who needed other IS to improve symptoms, or who required reduction of GC dosage, were prescribed tacrolimus, or other IS (not discussed in this study), based on the situation. Tacrolimus dosage was adjusted according to the individual's disease condition and tacrolimus concentration. Concisely, we prescribed 0.05 mg/kg/day tacrolimus (given twice daily) initially. The dose was increased to 0.1 mg/kg/day (a maximum of <4 mg/day) if symptoms did not improve sufficiently within days or a few months. No patient underwent thymectomy as clinicians and parents were more concerned about the role of the thymus in immune system development. Parents/guardians were prepared to delay thymectomy until the infants became adults [11]. We also collected post-treatment data to evaluate the safety of tacrolimus. Abnormal levels of T3, T4, thyroid-stimulating (TSH) hormones as well as thyroglobulin antibodies (TG-Ab) or thyroid peroxidase antibodies (TPO-Ab) were collectively termed thyroid-related abnormalities.

Efficacy and safety evaluation

GC dose and MG-ADL were evaluated at baseline (on tacrolimus initiation) and at last follow-up to evaluate tacrolimus efficacy. MGFA PIS was used to evaluate patients' outcomes. Patients were divided into groups according to the treatment outcome based on MGFA PIS: (i) the group of patients who achieved therapeutic goal: including Complete Stable Remission (CSR), Pharmacologic Remission (PR) and Minimal Manifestation (MM) and (ii) the group of patients who did not achieve therapeutic goal: comprising Improved (I), Unchanged (U), Worse (W), Exacerbation (E) and Died (D). GC dosages at last follow-up and prior to tacrolimus initiation were recorded. Based on patient medical records, we

compared clinical characteristics including age of symptom onset, gender, JMG subtype (ocular myasthenia gravis [OMG] vs. generalized myasthenia gravis [GMG]) and RNS status. Other variables compared comprised thyroid-related abnormalities, interval from disease onset to GC initiation, and interval from disease onset to tacrolimus initiation between the group of patients who achieved therapeutic goal and the group of patients who did not achieve therapeutic goal to detect determinants of tacrolimus efficacy. We compared the treatment outcome between groups of patients who achieved therapeutic goal versus those who did not achieve therapeutic goal at different timepoints (≤3 months vs. >3 months, ≤6 months vs. >6 months, ≤1 year vs. >1 year, ≤2 years vs. >2 years, ≤3 years vs. >3 years and ≤4 years vs. >4 years). Moreover, comparisons of clinical features between groups of patients treated with tacrolimus within or after 1 year from JMG onset were performed.

Statistical analysis

The data were processed using SPSS Version 27 software. Pearson's χ^2 test was used to compare categorical variables and the Mann–Whitney test was used to compare non-parametric continuous data.

RESULTS

Clinical characteristics of JMG patients

We were able to recruit 43 patients who met our diagnostic criteria of which 17 (39.53%) were males. Mean age at onset was 53.67 ± 41.43 SD (range, 10.0–150.0) months. Thirty-nine patients were screened for the presence of antibodies, and 64.1% (25/39) tested positive for the AChR-Ab and 7.69% (3/39) for the MuSK-Ab. Twenty-nine cases underwent a RNS test and 12 (41.38%) had abnormal neurophysiology. Thyroid-related abnormalities were detected in 13 of the 42 cases tested. Thirty-six cases underwent thymus screening by CT scan and six (16.7%) showed hyperplasia and three were suspected to have thymoma previously but this suspicion was ruled out after the next follow-up years. OMG was diagnosed in 22 (51.16%) cases and GMG in 21 (48.84%) cases. The mean duration of follow-up from JMG onset was 52.43 ± 31.51 (range, 12–120) months. Table 1 summarizes this information.

General treatment information and outcomes

Considering the whole cohort, the mean interval from JMG onset to GC initiation was 10.17 ± 21.00 (range, 0.0–100.00) months.

TABLE 1 Clinical characteristics of juvenile myasthenia gravis patients ($N = 43$).

Characteristic	Patients (*n*)	Percentage (%)
Gender		
Male	17	39.5
Female	26	60.5
Age at onset (years)		
<1	2	4.65
1–3	21	48.83
3–7	13	28.26
7–10	1	2.32
>10	6	13.95
Mean age at onset (months)	53.67 ± 41.43 (range, 10.0–150.0)	NA
Autoantibody test		
MuSK-Ab ($n = 39$)	3/39	7.69
AChR-Ab ($n = 39$)	25/39	64.10
Abnormal RNS ($n = 29$)	12/29	41.38
Thyroid-related abnormalities ($n = 42$)	13/42	30.95
Thymus hyperplasia ($n = 36$)	6/36	16.67
JMG subtype		
Patients with OMG	22/43	51.16
Patients with GMG	21/43	48.84
Mean duration of follow-up from JMG onset (months)	52.43 ± 31.51 (range, 12–120)	NA

Abbreviations: AChR-Ab, acetylcholine receptor antibody; GMG, generalized myasthenia gravis; JMG, juvenile myasthenia gravis; MuSK-Ab, muscle-specific tyrosine kinase antibody; NA, not applicable; OMG, ocular myasthenia gravis; RNS, repetitive nerve stimulation.

The mean interval from JMG onset to tacrolimus initiation was 26.25 ± 28.44 (range, 1.0–109.0) months. However, GMG patients received both GC and tacrolimus earlier than OMG cases. The mean interval from disease onset to GC initiation for GMG patients was 5.74 ± 9.95 (range, 0.23–36.5) months; in contrast, the mean interval from disease onset to GC initiation for OMG cases was 14.41 ± 27.35 (range, 0.0–100.0) months. The mean interval from disease onset to tacrolimus initiation for GMG patients was 16.27 ± 26.44 (range, 1.0–103.0) months, whereas the mean interval from disease onset to tacrolimus initiation for OMG individuals was 35.77 ± 27.53 (range, 2.0–109.0) months. Concerning prescriptions, tacrolimus enabled reduction of GC dosages for 28 (65.12%) cases and 15 (34.88%) cases had completely discontinued GC at last follow-up. The mean GC dose before tacrolimus initiation was 15.58 ± 8.66 (range, 5.0–40.0) mg/day while the mean GC dose at last follow-up was 5.00 ± 5.18 (range, 0.0–20.00) mg/day. The mean tacrolimus concentration during follow-up was 2.481 ± 1.70 (range, 0.5–6.9) ng/mL. At the last follow-up, 28 (65.12%) patients achieved therapeutic goal while 15 (34.89%) did not achieve therapeutic goal. The mean duration of

TABLE 2 Comparison of clinical characteristics of patients who did and did not achieve therapeutic goal.

Characteristic	Group of patients who achieved therapeutic goal (%) (*N* = 28)	Group of patients who did not achieve therapeutic goal (%) (*N* = 15)	c2/Z value	*P*-value
Gender				
Male	42.9 (12/28)	33.3 (5/15)	NA	0.745
Female	57.1 (16/28)	66.7 (10/15)		
JMG subtype				
Patients with OMG	32.1 (9/28)	86.7 (13/15)	NA	0.001
Patients with GMG	67.9 (19/28)	13.3 (2/15)		
Age at tacrolimus initiation for 34 cases who had MG-ADL (months)				
24–36	15.0 (3/20)	14.3 (2/14)	−0.057	0.955
37–48	5.0 (1/20)	21.4 (3/14)	−1.442	0.149
49–60	5.0 (1/20)	14.3 (2/14)	−0.926	0.355
≥61	75.0 (15/20)	50.0 (7/14)	−1.479	0.139
Abnormal RNS	55.0 (11/20)	11.1 (1/9)	−2.181	0.029
Thyroid-related abnormalities	25.0 (7/28)	42.9 (6/14)	−1.166	0.362
MuSK-Ab	11.5 (3/26)	0.0 (0/13)	−1.258	0.208
AChR-Ab	73.1 (19/26)	46.2 (6/13)	−1.631	0.103
Thymus hyperplasia	12.5 (3/24)	25.0 (3/12)	−935	0.350
Interval from JMG onset to tacrolimus initiation				
≤3 months	28.6 (8/28)	6.7 (1/14)	NA	0.129
≤6 months	39.3 (11/28)	13.3 (2/15)	NA	0.096
≤1 year	57.1 (16/28)	20.0 (3/15)	NA	0.026
≤2 years	75.0 (21/28)	40.0 (6/15)	NA	0.045
≤3 years	85.7 (24/28)	53.3 (8/15)	NA	0.031
≤4 years	92.9 (26/28)	66.7 (10/15)	NA	0.040
Duration from JMG onset to GC use (months), median (range)	2.00 ± 9.61 (0.0–36.5)	2.00 ± 32.44 (0.0–100.0)	−0.472	0.637
Duration from JMG onset to tacrolimus use (months), median (range)	10.500 ± 19.15 (1.0–78.0)	36.00 ± 35.72 (2–109)	−2.589	0.010
MG-ADL score at tacrolimus initiation for 34 cases, median (range)	4 ± 2.447 (2–11)	2.00 ± 2.774 (1–12)	−2.062	0.039
MG-ADL score at last follow-up for 34 cases, median (range)	0.00 (0–0)	1.00 ± 1.225 (0–4)	−4.124	< 0.001
MG-ADL score change for 34 cases, median (range)	4 ± 2.447 (2–11)	1.00 ± 2.160 (0–8)	−2.935	0.003

Abbreviations: AChR-Ab, acetylcholine receptor antibody; GC, glucocorticoids; GMG, generalized myasthenia gravis; JMG, juvenile myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MuSK-Ab, muscle-specific tyrosine kinase antibody; NA, not applicable; OMG, ocular myasthenia gravis; RNS, repetitive nerve stimulation.

follow-up from tacrolimus initiation was 33.47 ± 22.28 (range, 3–89) months.

Determinants of the achievement of therapeutic goal

To determine factors associated with the achievement of therapeutic goal, we compared clinical characteristics between groups of patients who achieved therapeutic goal and patients who did not achieve therapeutic goal. GMG subtype had a statistically significant association with a group of the patients who achieved therapeutic goal ($p = 0.001$). Abnormal RNS showed a relationship with a group of the patients who achieved therapeutic goal ($p = 0.029$). Patients who achieved therapeutic goal received tacrolimus earlier than patients who did not achieve therapeutic goal. Median duration from JMG onset to tacrolimus use was 10.500 ± 19.15 (range, 1.0–78.0) months for those who achieved therapeutic goal versus 36.00 ± 35.72 (range, 2–109) months for those who did not achieve therapeutic goal ($p = 0.010$). MG-ADL scores were assessed at tacrolimus initiation and at last follow-up for 34 patients: 16 were diagnosed with GMG and 18 OMG. The baseline MG-ADL scores were assessed when 12 (35.29%) patients were aged ≤5 years and 64.70% were aged >5 years. Of those aged ≤5 years, five cases were aged between 24 and 36 months, four cases were between 37 and 48 months and three cases were between 49 and 60 months. We observed that a higher proportion of patients with high MG-ADL scores at tacrolimus initiation achieved therapeutic goal than those with low scores. The median MG-ADL score at tacrolimus commencement was 4 ± 2.447 (range, 2–11) for patients who achieved therapeutic goal and 2.00 ± 2.774 (range, 1–12) for patients who did not achieve therapeutic goal ($p = 0.039$). The median MG-ADL score at last follow-up was 0.00 (range, 0–0) for patients who achieved therapeutic goal and 1.00 ± 1.225 (range, 0–4) for patients who did not achieve therapeutic goal ($p = <0.001$). The median MG-ADL score change was 4 ± 2.447 (range, 2–11) for patients who achieved therapeutic goal and 1.00 ± 2.160 (range, 0–8) for patients who did not achieve therapeutic goal ($p = 0.003$). Table 2 summarizes this information.

Comparison of clinical characteristics of patients treated with tacrolimus within or after 1 year from onset

We tried to investigate the proper timing for tacrolimus treatment at last follow-up by comparing the clinical features between subgroups of patients treated with tacrolimus within or after 1 year. However, before selecting the cut-off time of 1 year, we compared treatment outcomes between groups of patients who achieved therapeutic goal and those who did not achieve therapeutic goal at different timepoints. The compared timelines included ≤3 months versus >3 months, ≤6 months versus >6 months, ≤1 year versus >1 year, ≤2 years versus >2 years, ≤3 years versus >3 years, and ≤4 years versus >4 years. Consequently, we found that a group of patients who achieved therapeutic goal showed significant correlations with tacrolimus treatment received at ≤1 year (57.1% vs. 20.0%, $p = 0.026$), at ≤2 years (75.0% vs. 40.0%, $p = 0.045$), at ≤3 years (85.7% vs. 53.3%, $p = 0.031$) and at ≤4 years (92.9% vs. 66.7%, $p = 0.040$). Table 2 summarizes this information. Although four timepoints demonstrated associations with the group of patients who achieved therapeutic goal, we opted for the cut-off time of 1 year because it showed a stronger correlation and might reduce too much exposure to GC, which has many side effects.

We found that 84.2% (16/19) of patients who received tacrolimus within 1 year achieved therapeutic goal and only 15.8% (3/19) of patients who received tacrolimus within this timepoint did not achieve therapeutic goal ($p = 0.026$). GMG subtype showed an association with a group of patients who received tacrolimus within 1 year ($p = <0.001$). Table 3 summarizes this information.

Tacrolimus side effects

Of the 43 cases that received tacrolimus, 14 cases experienced mild transient side effects. Transient mild hyperlipidemia was found in 10 cases, hair loss was observed in one patient, transient mild increase of total bilirubin was found in one case and transient elevation of

TABLE 3 Comparison of clinical characteristics between patients treated with tacrolimus within or after 1 year.

Characteristic	Patients treated with tacrolimus within ≤1 year (%)	Patients treated with tacrolimus after 1 year (%)	c2/Z value	*P*-value
Gender				
Male	42.1 (8/19)	37.5 (9/24)	NA	1.000
Female	57.9 (11/19)	62.5 (15/24)		
JMG type				
GMG	78.9 (15/19)	25.0 (6/24)	NA	<0.001
OMG	21.1 (4/19)	75.0 (18/24)		
Outcome				
Patients who achieved therapeutic target	84.2 (16/19)	50.0 (12/24)	NA	0.026
Patients who did not achieve therapeutic target	15.8 (3/19)	50.0 (12/24)		

Abbreviations: GMG, generalized myasthenia gravis; JMG, juvenile myasthenia gravis; NA, not applicable; OMG, ocular myasthenia gravis.

aspartate aminotransferase was found in one patient. No patient experienced severe side effects that necessitated discontinuation of therapy.

DISCUSSION

In this study, our aim was to investigate the proper timing, efficacy and safety of tacrolimus for the management of JMG, especially GC-dependent or GC-resistant cases. All our 43 patients were treated with oral pyridostigmine and GC prior to tacrolimus, and none of them received other IS or underwent thymectomy. This research has revealed several things regarding tacrolimus treatment for JMG. GMG patients were more likely to receive both GC and tacrolimus earlier than the corresponding OMG cases; GMG cases were more likely to achieve therapeutic goal than OMG cases. Tacrolimus helped both in the reduction of GC dosages as well as in discontinuation of GC for 34.88% of cases. Patients who achieved therapeutic goal received tacrolimus earlier than those who did not achieve therapeutic goal. A higher proportion of patients with high MG-ADL scores at tacrolimus initiation achieved therapeutic goal than those with low scores. About 84.2% of patients who received tacrolimus within 1 year achieved therapeutic goal and only 15.8% of patients did not achieve therapeutic goal. Cases diagnosed with GMG were more likely to receive tacrolimus within 1 year than those diagnosed with OMG. Of the whole cohort, 65.12% of patients achieved therapeutic goal at the end of follow-up. Patients who achieved therapeutic goal were more likely to have abnormal RNS. Few cases experienced transient mild side effects from tacrolimus.

Tacrolimus helped in both reduction of GC dosages as well as discontinuation of GC for some patients, a finding that is similar to those of two other previous studies [4, 7]. In addition, our study demonstrated that tacrolimus improved the quality of life of patients as reflected by their MG-ADL scores. In our study, the mean MG-ADL score before tacrolimus initiation was 3.65 ± 2.60 and the mean GC dose before tacrolimus initiation was 15.58 ± 8.66 mg/day. Respectively, the mean MG-ADL score at last follow-up was 0.33 ± 0.829 and the mean GC dose at last follow-up was 5.00 ± 5.18 mg/day. In a Chinese study of 14 GMG cases, the MG-ADL score before the initiation of tacrolimus was 5.08 ± 2.36 while the GC dose was 26.15 ± 14.02 mg/day, and at the end of 1 year's follow-up treatment with tacrolimus, the GC dosage was 1.15 ± 2.19 mg/day while the mean MG-ADL score was 1.38 ± 1.56 [4]. We have observed that a higher proportion of patients with a high MG-ADL score at tacrolimus initiation achieved therapeutic goal than those with a low score, as was observed in another Chinese study [4]; however, the reasons for this observation are currently are unknown. Most of our cases presented with OMG rather than GMG, as was the case in another previous Chinese study with 14 cases [4]. Interestingly, GMG patients were more likely to receive both GC and tacrolimus earlier than OMG cases; consequently, patients diagnosed with GMG were more likely to achieve therapeutic goal than OMG cases. It seems that clinicians are more likely to diagnose and treat GMG aggressively than OMG, which is in accordance with guidelines [2]. This also applies to patients with abnormal RNS who are usually more severe than those with normal RNS. The presence of thymus hyperplasia has been reported as an independent risk factor for poor efficacy of tacrolimus in steroid-resistant JMG even when thymectomy was performed according to one study [7] but we did not observe this in our study. In addition, the pre-intervention exacerbated status (exacerbated patients included patients who had previously achieved Minimal Manifestation (MM) or better status with steroid therapy) before tacrolimus initiation has also been reported as an independent risk factor for good efficacy of tacrolimus but we did not evaluate it in our study [7].

Patients who achieved therapeutic goal received tacrolimus earlier than patients who did not achieve therapeutic goal. Median duration from JMG onset to tacrolimus use was 10.500 ± 19.15 months for those who achieved therapeutic goal and 36.00 ± 35.72 months for those who did not achieve therapeutic goal. In another JMG Chinese study, the mean disease duration from JMG onset to tacrolimus use was 41.92 ± 39.97 months [4]. Tacrolimus was introduced earlier to our patients than in the previous study [4]. In our study, the mean interval from disease onset to GC initiation for GMG patients was 5.74 ± 9.95 (0.23–36.5) months; in contrast, the mean interval from disease onset to GC initiation for OMG patients was 14.41 ± 27.35 (0.0–100.0) months. The mean interval from disease onset to tacrolimus initiation for GMG patients was 16.27 ± 26.44 (1.0–103.0) months, whereas the mean interval from disease onset to tacrolimus initiation for OMG patients was 35.77 ± 27.53 (2.0–109.0) months. A Japanese study with nine OMG cases to assess the efficacy of tacrolimus showed that the mean disease duration from OMG onset to tacrolimus use was 18 (range, 8–27) months and the mean disease duration from OMG onset to GC use was 27 (range, 21–30) months [6]. Tacrolimus was introduced later to our OMG patients than in the Japanese study [6]. We administered 0.05–0.1 mg/kg/day tacrolimus; likewise, 0.05–0.2 mg/kg/day was used in a Japanese study that included nine OMG patients [6]. Consequently, we propose the administration of low-dose tacrolimus at an early stage for both OMG and GMG patients (within 1 year of disease onset).

A few cases experienced transient, mild, reversible side effects, a finding similar to another Chinese study with 14 JMG cases [4]. In the previous study, one case stopped using tacrolimus due to dizziness and nausea [4]; however, none of our patients in the present study stopped tacrolimus due to severe side effects. The mean tacrolimus concentration in our study was 2.481 ± 1.70 ng/mL, whereas it was 4.22 ± 0.98 ng/mL in another Chinese JMG study that involved 14 cases [4]. This concentration discrepancy may be due to the low dosages we used for our patients. The production of the AChR-Ab is T cell-dependent [12] and tacrolimus inhibits the activation and proliferation of T cells and reduces CD19+ BAFF-R+ B cells [13]. The present study has provided more evidence from a large sample size that the provision of tacrolimus at low dosages within 1 year of JMG onset is effective and safe.

Most of the previous studies reported the efficacy and safety of tacrolimus in adult patients, with some reporting on a mixture of adults and children [4–6].

Conclusively, to our knowledge, this is the first large-sample study to evaluate the proper timing, efficacy and safety of tacrolimus in a pure JMG cohort. This research has revealed that the provision of tacrolimus at low dosages within 1 year of JMG onset is effective and safe. It is recommended that tacrolimus should be administered sufficiently early for JMG including GMG and GC-dependent or GC-resistant OMG cases.

Study limitations

This study was conducted retrospectively, therefore it is prone to information bias. It also involved only a single center. We used the MG-ADL score for the outcome assessment of some patients aged <5 years, consequently the results might not be robust. Besides, the use of the MG-ADL scale in a young population with predominant OMG has some setbacks due to the diplopia question. However, due to the lack of another alternative scale for use in children we had no other option. Although there was no complete overlap of the administration of GC and tacrolimus in any patient, there was some close succession of treatment in a few cases. Therefore, patients in whom tacrolimus was initiated <6 months could have improved to some degree on account of steroid administration. The development of a robust outcome measure for children is needed, and prospective multicenter studies focused on tacrolimus alone are needed for treatment guidance.

AUTHOR CONTRIBUTIONS

Guoli Wang: Writing – original draft; writing – review and editing; visualization; validation; data curation; formal analysis; methodology; software; investigation. **Miriam Kessi:** Writing – original draft; visualization; validation; writing – review and editing; formal analysis; methodology; software. **Xi Huang:** Visualization; validation; data curation. **Wen Zhang:** Data curation; visualization; validation; funding acquisition. **Ciliu Zhang:** Data curation; validation; visualization; investigation. **Fang He:** Funding acquisition; validation; visualization; investigation; data curation. **Jing Peng:** Data curation; validation; visualization; investigation. **Fei Yin:** Validation; visualization; data curation; investigation; funding acquisition. **Lifen Yang:** Conceptualization; investigation; funding acquisition; writing – original draft; writing – review and editing; visualization; validation; methodology; formal analysis; supervision; data curation; project administration; resources.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflicts of interest to disclose. The manuscript was read and approved by all the authors, the requirements for authorship as stated in the journal guideline have been met, and each author believes that the manuscript represents honest work.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study including all methods adhered to the tenets of the Declaration of Helsinki and received approval (approval number 202310892) from the Institutional Review Board and Research Ethics Committee of Xiangya Hospital, Central South University, Changsha, Hunan, China. Written consents were obtained from the parents/guardians of the subjects, which were approved by the Institutional Ethics Committee of Xiangya Hospital, Central South University.

CONSENT FOR PUBLICATION

Written informed consent for publication of clinical details and clinical images were obtained from participants or their parents.

ORCID

Miriam Kessi https://orcid.org/0000-0002-7932-9292
Ciliu Zhang https://orcid.org/0000-0002-2230-9047
Fei Yin https://orcid.org/0000-0002-7192-6308
Lifen Yang https://orcid.org/0000-0003-2400-9539

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