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Early real-life experience on Zilucoplan for generalized myasthenia gravis: ZILU25 multicenter observational study

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ABSTRACT

Background and objectives: Generalized Myasthenia gravis (gMG) is a rare chronic autoimmune disease affecting the postsynaptic membrane of the neuromuscular junction. New treatment options, such as the C5 inhibitors, are growing with promising results. In this study we investigated the real-world use of Zilucoplan for AChR-positive gMG in Italy.

Materials and methods: Zilucoplan was self-administered by daily subcutaneous injections. Efficacy was assessed by Myasthenia Gravis Foundation of America Post-intervention status (MGFA-PIS), Myasthenia Gravis Activity of Daily Living (MG-ADL), Myasthenia Gravis Composite (MGC), Myasthenia Gravis quantitative (QMG) scales and 15-items Myasthenia Gravis Quality of Life (MG-QOL-15) questionnaire at baseline and after 1, 4, 12, 24 and 48 weeks.

Results: 54 patients (37 females, aged 57.3) received zilucoplan with a mean follow-up of 26.4 weeks. We observed a clinical meaningful and significant reduction of MG-ADL, QMG, MGC and MG-QOL-15 scores from W4 to W12 and sustained at W24 of follow-up. The MG-ADL responder rate was 75.6 % at W12 and 82.9 % at W24. Minimal symptoms expression (MSE) was obtained in 55.6 % of patients at W48 with a mean reduction of the daily prednisone dose of 8.3 mg at W24. Chronic IVIg was associated to a better response to MG-ADL at W12 at multivariate analysis.

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Discussion and conclusions: Zilucoplan was well-tolerated and effective in most patients with AChR-positive gMG. A clinical meaningful effect was reported since the first week and was sustained after 24 weeks. Further studies are needed to confirm these preliminary real-life data.

1. Introduction

Myasthenia Gravis (gMG) is a chronic autoimmune neuromuscular disorder characterized by fluctuating muscle weakness and fatigability, which results from the impairment of neuromuscular transmission due to the presence of antibodies against acetylcholine receptors (AChRs) or other components of the neuromuscular junction [1]. MG is classified into different subtypes depending on the age at dis- ease onset ("early onset," EO before 50 years; "late onset," LO after 50 years), the distribution of weakness ("ocular," oMG; "generalized," gMG), the presence of thymoma, and the response to treatments (classical forms versus refractory MG). Despite recent advancements in the standard of care, many patients with AChRAb positive MG continue to experience debilitating symptoms and may not respond adequately to conventional therapies, such as acetylcholinesterase inhibitors, corticosteroids (CS), and nonsteroidal immunosuppressants (NSISTs) and thymectomy [2,3]. The latter conventional immunomodulating treatments act non-specifically on the immune system and are source of severe adverse events, both in the short and long term, which limits their use, particularly CS; moreover, NSISTs are associated with a long delay between treatment start and measurable effect, which is typically observed after 6–12-month [4–6]. Hence, several unmet needs from conventional treatment in MG remain unaddressed [5]. In last years, innovative targeted and more specific therapy are emerging for generalized MG (gMG). Complement activation is central to the pathogenesis of Myasthenia Gravis (MG), damaging the postsynaptic NMJ membrane and reducing the number of exposed AChR (Howard, 2018). In recent years, intravenous C5-inhibitors have been investigated showing clinical efficacy with good safety profiles [7,8]. Real-life experience documented a heterogeneous clinical response to complement inhibition, highlighting the need for reliable predictive factors [9,10]. Zilucoplan is a macrocyclic peptide for subcutaneously self-administration [11], representing an innovation in the landscape of gMG treatments [12]. Zilucoplan binds to C5 with high affinity and specificity, preventing its cleavage to C5a and C5b. Additionally, by binding to the C5b, zilucoplan sterically hinders binding of C5b to C6, which prevents the subsequent assembly and activity of the membrane attack complex, thereby reducing complement-mediated damage at the neuromuscular junction [11]. As a peptide with a dual mechanism of action, and having the ability for subcutaneous self-administration, this novel approach offers the potential for significant symptom improvement in patients who are refractory to traditional treatments [11]. Clinical studies, including the phase 3 trial RAISE, have demonstrated that Zilucoplan can improve muscle strength, and enhance the overall quality of life for individuals with AChR-positive gMG [13].

2. Methods

2.1. Ethical approval

The study was approved by the competent Ethical Committee ("Comitato Etico Territoriale Regione Sicilia") on 6th February 2025 (V n.6/2025), and it was conducted in conformity with the Declaration of Helsinki principles. The study was registered on the RSO national AIFA platform ("Registro Studi Osservazionali", ID2473 Cod. ZILU25). All participating centres obtained written consent from each patient for the use of anonymized clinical data for research purposes.

2.2. Study design and inclusion criteria

We carried out a multicentre, observational, retrospective study to assess the safety and effectiveness of zilucoplan in patients with generalized myasthenia gravis (gMG) within a real-world clinical context. This study was part of the Early Access Program (EAP MG0025IT, V. 12th July 2023), designed to offer eligible gMG patients access to zilucoplan treatment prior to its regulatory approval. Thirteen specialized Italian referral centers for myasthenia gravis took part in the study. Inclusion criteria for the study were: 1) treatment with zilucoplan as part of routine clinical practice started under the EAP program; 2) age of 18 years or older at the time of informed consent and treatment initiation; 3) Myasthenia Gravis Foundation of America (MGFA) classification IIa, IIb, IIIa, IIIb, IVa, IVb; 4) Post-Intervention Status Unchanged or Worsened after treatment with CS and/or one other NSIST, administered at adequate dosages and for a sufficient duration, but with persistent symptoms or side effects that impaired functionality, or that contraindicate CS and/or NSIST treatment, as assessed by both the patient and the treating physician, in line with the requirements of the EAP; 5) A minimum follow-up of 4 weeks from the initiation of zilucoplan treatment. Patients previously enrolled in the RAISE trial were excluded.

2.3. Treatment schedule

Zilucoplan was administered by daily subcutaneous self-injection with a dose of 0.3 mg/kg (16.6 mg, 23 mg, or 32.4 mg prefilled syringes, depending on body weight). If clinically necessary due to worsening symptoms or the risk of myasthenic crisis (MC), patients were permitted to receive IVIg or PLEX as rescue therapy alongside zilucoplan. Zilucoplan was supplied by UCB as part of the EAP in Italy.

2.4. Vaccinations

Before starting zilucoplan, all patients were vaccinated against *Neisseria meningitidis* serogroups A, C, W135, Y, and B, with vaccinations administered at least 14 days before the first dose. Alternatively, patients who had not completed the vaccination schedule received appropriate prophylactic antibiotics before starting treatment, which were continued until the vaccination regimen was completed.

2.5. Data collection

Data were collected retrospectively from medical records at each participating center between January and March 2025. Local databases were used as the primary source for data extraction. A standardized template, with predefined criteria for data categorization, was distributed across all participating centers. Subsequently, the collected data were consolidated into a single centralized database and prepared for analysis. The following variables were included in the data collection set: current age, gender, and body weight; comorbidities; age at onset of MG ("early onset," before 50 years; "late onset," after 50 years) and age at treatment initiation; disease duration at baseline; MGFA clinical classification at disease onset and at baseline; history of thymectomy and thymic status; previous treatments, including prednisone and NSIST with relative dosage, biological other than zilucoplan and chronic IVIg (defined as a treatment with IVIg more than 3 times a year or more frequently) or PLEX, as well as the number of cycles administered during the year before starting zilucoplan; history of prior myasthenic exacerbations and/or myasthenic crisis (MC), hospitalizations and any use of rescue therapies. Dosages of prednisone and NSIST were recorded at

baseline. Further changes in the dosages of ongoing baseline medications, adverse events, treatment discontinuation, and the use of rescue therapies were also recorded during the treatment with zilucoplan. Efficacy was assessed by Myasthenia Gravis-Activities of Daily Living Profile (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scales before the start of the treatment and after 1, 4, 12, 24, and 48 weeks.

2.6. Clinical scales and outcome measures

The following clinical scales, specific to gMG were administered by trained clinicians, accordingly to each centre clinical practice and EAP indications: (i) MG-ADL (ii) QMG, and (iii) Myasthenia Gravis Composite (MGC). Clinical scales were administered at baseline and after 1, 4, 12, 24, and 48 weeks. We retrospectively collected data at baseline and at each time point, up to the most recent follow-up, across all participating centres. Minimal symptom expression (MSE) as defined as MG-ADL $\leq$1 was assessed for each patient at the end of the clinical follow-up. Changes in MG-ADL and QMG scores over time were the primary outcome measures of the study to evaluate the efficacy of zilucoplan treatment. Patients were classified as responders if they demonstrated a reduction of at least 3 points in the MG-ADL score (MG-ADL responders) and a reduction of at least 5 points in the QMG score (QMG-responders) at each time point of the follow-up. Quality of life was measured with the Myasthenia Gravis Quality of Life 15 questionnaire (MG-QOL-15). MGFA post-intervention status (MGFA-PIS) was recorded at each time point [14]. The patient was defined in "Complete Stable Remission" (CSR) in the absence of symptoms or signs of MG while receiving no therapy for MG during that time; Pharmacologic Remission (PR) was defined by the same criteria as for CSR except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness. Minimal Manifestations (MM) status was defined as a patient with no symptoms of functional limitations from MG but has some weakness on examination of some muscles; this class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination. MM-0 indicated a patient who had received no MG treatment; the patient usually continues to receive some form of immunosuppression but no cholinesterase inhibitors or other symptomatic therapy; MM-2 represented a patient who had received only low-dose cholinesterase inhibitors (<120 mg pyridostigmine/day); MM-3 displayed a patient who had received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression. Improved (I) was defined by a substantial decrease in pretreatment clinical manifestations or a sustained substantial reduction in MG medications. Unchanged (U) status was defined as no substantial change in pretreatment clinical manifestations or reduction in MG medications. Worse (W) status was represented by a substantial increase in pretreatment clinical manifestations or a substantial increase in MG medications. Exacerbation (E) was reported when a patient who have fulfilled criteria of CSR, PR, or MM subsequently developed clinical findings greater than permitted by these criteria. Died of MG (D of MG) were patients who died of MG, of complications of MG therapy [14]. MGFA-PIS was defined comparing the status at baseline and at each time point. Secondary outcome measures included tapering of prednisone and NSIST during follow-up, as well as the comparison of the need for IVIg or PLEX cycles in the year before and during zilucoplan treatment. We defined gMG as "refractory" after treatment with two or more immunosuppressive therapies before receiving zilucoplan, or at least one immunosuppressive therapy with intravenous immunoglobulin or plasma exchange given at least four times per year, for 12 months without symptom control [7,15,16]. We evaluated safety by monitoring and documenting treatment-emergent adverse events throughout the study period. We recorded exacerbation, as well as rescue medication use, and MC from baseline to last follow-up.

2.7. Statistical analysis

We provide a descriptive analysis for demographic characteristics and baseline variables. This included frequency and percentage for categorical variables, median and interquartile range (IQR) or mean $\pm$ standard deviation (SD), for continuous variables. Unless otherwise stated, we also calculated 95 % CI of the mean to compare our data with those of other studies. As patients entered the intervention at different times and their follow-up at the time of this study was highly variable, ranging from 4 to 48 weeks (mean 26.4 $\pm$ 16.7), we performed a missing value analysis. The percentage of missing data across the time points of evaluation from week 1 to week 48 ranged from 0 to 67 % for both MG-ADL and QMG and, in total, 134 records out of 660 (20 %) were incomplete. Also, as only 18 patients had completed 48 weeks of follow-up at the time of the analysis and given that up to week 24, the percentage of missing data was quite low (11 %, 61 out of 550: 11 patients with missing data at week 12 (9 for MG-ADL and 11 for QMG), 19 with missing data at week 24 (19 for MG-ADL and 19 for QMG), and 36 patients had no missing data at week 24), we evaluated MG-ADL and QMG scores at weeks 1, 4, 12 and 24 for statistical analysis. To determine whether the missing value process was random, and the imputation was safe, we used the missing completely at random (MCAR) test (excluding patients who discontinued treatments because of side effects). The comparison between the variance of valid cases and missing value cases across both variables MG-ADL, QMG, MGC, and MG-QOL-15 at weeks 1, 4, 12, 24, and 48 was non-significant. The presence of outliers and the normality of the distribution of MG-ADL and QMG scores were tested using a boxplot and the Shapiro-Wilk test, respectively. If the variables had no outliers and were normally distributed, a one-way repeated measures ANOVA was performed to determine whether there were statistically significant changes from baseline throughout the intervention. Otherwise, the non-parametric Friedman test with Bonferroni correction for multiple comparisons was used for statistical analysis. For the one-way repeated measures ANOVA, sphericity was tested by Mauchly's test and, when it was violated, the ANOVA was corrected by Greenhouse and Geisser test. Cochran's Q test was used to compare the MG-ADL and QMG responders' rate across the different timepoints. Post-hoc analyses were performed using McNemar tests (Bonferroni-corrected). Survival analysis with Kaplan-Meier method was performed considering follow-up and time of discontinuation. Mantel-Cox was calculated comparing Kaplan-Meier curves using as factors the presence of comorbidity, disease duration, age at disease onset, thymoma, refractoriness, sex, and zilucoplan dosage. To identify possible predictors of response to zilucoplan, an unconditional logistic regression analysis was performed for each study variable, considering the MG-ADL response to W12 as the outcome variable. The choice of the response on MG-ADL at W12 comes from the clinical observation that a stable and meaningful response to complement inhibitors is usually obtained after three months of treatments [7,8,17]. The odds ratios (OR) with 95 % confidence intervals (CI) and p value (two-tailed test, $\alpha = 0.05$) were calculated. Multivariate analysis was performed to investigate the independent effect of a risk or protective factor after adjustment for one or several other factors or to adjust for confounding variables. Parameters associated with the outcome at the univariate analysis with a threshold of $p = 0.10$ were included in the multivariate model. MG-ADL and QMG at baseline were considered a priori confounders, regardless of the level of significance. The model was manually constructed using the likelihood ratio test (LRT) to compare the log-likelihood of the model with and without a specific variable. Likewise, other associations between putative independent predictors and the dependent variable were assessed by performing univariate and multivariate logistic regression models. Significance was set at 0.05, two-tailed. Statistical analysis was performed using SPSS version 26.

3. Results

3.1. Patients' demographic and clinical characteristics at baseline

Fifty-four patients were treated with Zilucoplan and followed up from 4 to 48 weeks. The mean age was 57.5 ± 14.5 years with 69 % of females, and a high burden of comorbidity (93 %). Early onset MG was reported in 54 % of patients with a mean age at disease onset of 46.8 ± 17.8 and an average disease duration of 10.7 years. Thymoma was reported in 41 % of patients (Table 1).

Table 1
Main baseline demographic and clinical characteristics of patients treated with zilucoplan. Continuous variables are expressed as mean with standard deviation (in brackets) and categorical variables as numeric count and percentages. IVIg, Intravenous immunoglobulins; FcRn, neonatal fragment crystallizable receptor; MGFA, Myasthenia Gravis Foundation of America; MG-ADL, Myasthenia Gravis Activity of Daily Living; MGC, Myasthenia Gravis Composite; MG-QOL-15, 15-item Myasthenia Gravis Quality of Life questionnaire; PLEX, plasma exchange; QMG, Myasthenia Gravis quantitative scale.

Clinical variable	Total ($N = 54$)
Age (years old)	57.5 (14.5)
Age at onset	46.8 (17.8)
Sex (female %)	37 (69 %)
Body Weight (Kg)	81.1 (20.5)
Disease duration (years)	10.7 (9.6)
Previous thymectomy (n, %)	31 (57 %)
Diagnosis of thymoma (n, %)	22 (41 %)
Comorbidity (n, %)	50 (93 %)
Number of comorbidities	3.3 (1.9)
Treatment refractory (n, %)	30 (56 %)
Prednisone dose at baseline (mg/day)	20.5 (13.1)
MG-ADL at baseline	8.0 (3.0)
QMG at baseline	13.9 (5.2)
MGC at baseline	14.1 (7.0)
MG-QOL-15 at baseline	21.2 (14.2)
Hospitalizations previous year (n, %)	28 (52 %)
Rescue therapy previous year (n, %)	45 (83 %)
Concomitant treatments at baseline	
Pyridostigmine (n, %)	53 (98 %)
Prednisone (n, %)	53 (98 %)
Azathioprine (n, %)	39 (72 %)
Chronic IVIg (n, %)	35 (65 %)
Long term PLEX (n, %)	19 (35 %)
Mycophenolate mofetil (n, %)	18 (33 %)
FcRn Inhibitors (n, %)	8 (15 %)
Cyclosporin (n, %)	7 (13 %)
Complement Inhibitors (n, %)	4 (7 %)
Methotrexate (n, %)	1 (2 %)
Rituximab (n, %)	1 (2 %)
MG subtype (onset)	
Early onset (n, %)	29 (54 %)
Late onset (n, %)	25 (46 %)
MGFA baseline	
IIA (n, %)	5 (9 %)
IIB (n, %)	14 (26 %)
IIIA (n, %)	15 (28 %)
IIIB (n, %)	14 (26 %)
IVA (n, %)	2 (4 %)
IVB (n, %)	4 (7 %)
Zilucoplan dose	
16.6 mg (n, %)	5 (9 %)
23 mg (n, %)	21 (39 %)
32.4 mg (n, %)	28 (52 %)
Follow-up with zilucoplan (weeks)	26.4 (16.7)

3.2. Changes in clinical scale scores during follow-up

Overall, Zilucoplan improved the scores in clinical scales and questionnaires with a significant reduction in prednisone dose when comparing baseline data to the 24 weeks follow-up. Table 2 describes the reduction of MG-ADL, QMG, and MGC scores since the start of zilucoplan, as well as the reduction of CS dosage. Fig. 1 reports the effects of zilucoplan on MG-ADL, QMG, MGC and MG-QOL-15 across different time points.

3.3. MG-ADL score

We found a significant reduction of MG-ADL scores was reported from baseline to W24 (F 22.2, $p = 0.002$, Fig. 1A).

The reduction was already evident at W1 and peaked at W24. The effect was no different depending on the presence of comorbidity, disease duration, age at disease onset, thymoma, refractoriness, gender and zilucoplan dosage (Supplementary Fig. 1-7).

3.4. MG-ADL responders

MG-ADL responder rates were reported between 35.2 at W1 and 88.9 % at W48 (Table 3). Cochran's Q test revealed a significant difference in responder rates across the different timepoints ($Q = 26.5$, df $= 4$, $p < 0.001$). Post-hoc analyses using McNemar tests (Bonferroni-corrected $\alpha = 0.0125$) showed a significant difference between W1 and W4 ($p < 0.001$), W1 and W12 ($p < 0.001$), W1 and W24 ($p < 0.001$), but not between W4 and W12 ($p = 0.34$), W4 and W24 ($p = 0.34$), or W12 and W24 ($p = 1.00$).

3.5. MSE

MSE was defined as an MG-ADL score of 0 or 1. The proportion of patients with MSE ranged from 7.4 % at W1 to 55.6 % at W48 (Table 3). Cochran's Q test revealed a significant difference in responder rates across the different timepoints ($Q = 25.47$, df $= 4$, $p < 0.001$). Post-hoc analyses using McNemar tests (Bonferroni-corrected $\alpha = 0.0125$) showed a significant difference between W1 and W12 ($p = 0.001$), W1 and W24 ($p < 0.001$), W4 and W12 ($p = 0.021$), W4 and W24 ($p = 0.002$), but not between W1 and W4 ($p = 0.125$), or W12 and W24 ($p = 0.727$).

Table 2
MG-ADL and QMG baseline mean values and differences of the means of patients who completed the 24-week follow-up: 36 patients for MG-ADL, QMG and prednisone and for 16 patients for MGC. Values are expressed as mean ± SD, ranges, and 95 %CI. MG-ADL, Myasthenia Gravis Activity of Daily Living; MGC, Myasthenia Gravis Composite; QMG, Quantitative Myasthenia Gravis; § Mean score at baseline and mean difference with respect to baseline during follow-up; ° Mean dosage at baseline and mean dosage change during follow-up.

	Baseline	Week 1	Week 4	Week 12	Week 24
MG-ADL § (SD; ranges)	8.34 (0.44, from 0 to 14)	-2.00 (0.38, from 2 to -7)	-3.94 (0.46, from 2 to -11)	-5.08 (0.49, from 2 to -10)	-5.46 (0.58, from 3 to -12)
QMG § (SD; ranges)	14.58 (0.79, from 3 to 26)	-1.76 (0.42, from 6 to -7)	-4.18 (0.55, from 7 to -11)	-6.15 (0.84, from 2 to -18)	-5.88 (0.94, from 8 to -16)
MGC § (SD; ranges)	14.96 (1.35, from 1 to 33)	-1.92 (1.31, from 5 to -21)	-6.54 (0.73, from 6 to -27)	-8.04 (1.23, from 11 to -28)	-7.88 (1.10, from 7 to -25)
Prednisone ° (SD; ranges)	20.74 (2.34, from 0 to 65)	-0.97 (0.43, from 0 to -10)	-2.64 (0.66, from 0 to -15)	-5.42 (0.93, from 0 to -20)	-8.38 (1.49, from 5 to -25)

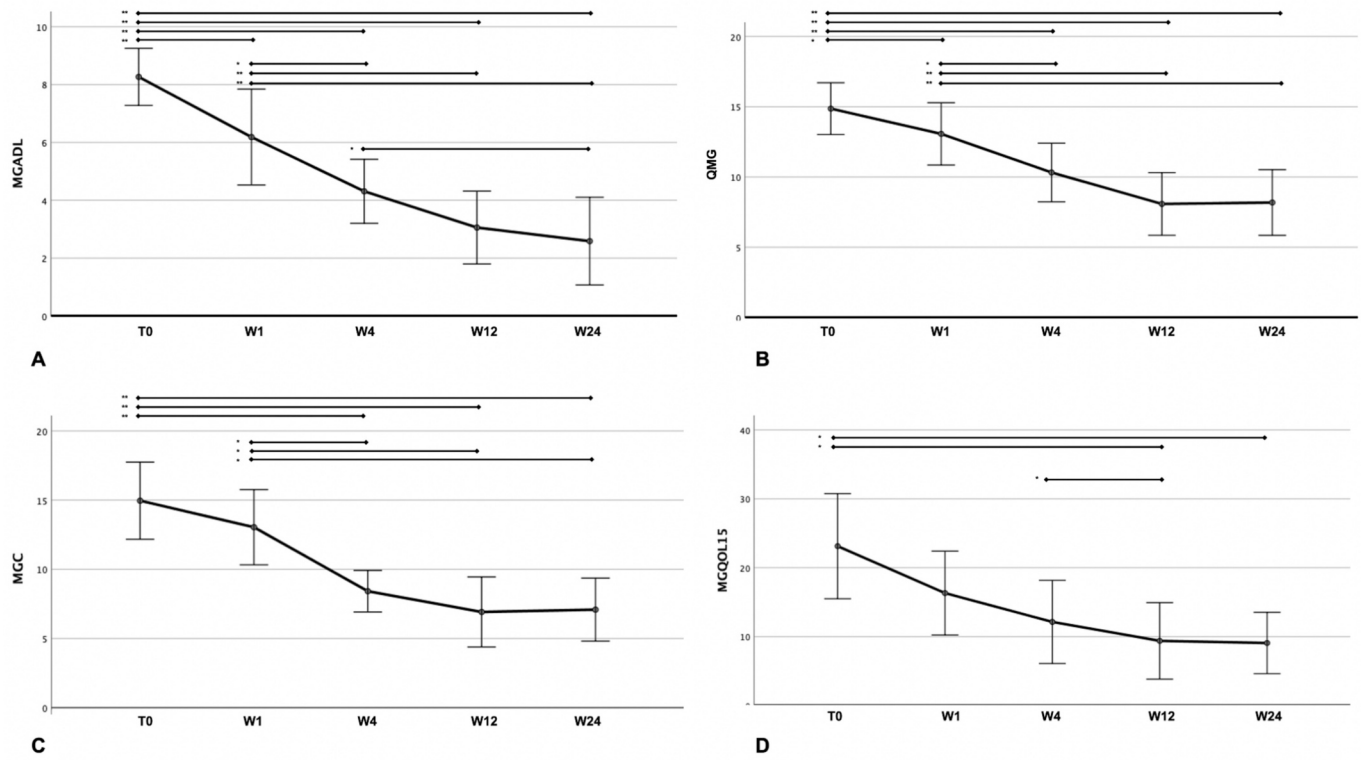

Fig. 1. MG-ADL, QMG, MGC, and MG-QOL-15 mean changes during the first 24 weeks of Zilucoplan treatment in patients with anti-AChR gMG. Top: clinical effect of zilucoplan on MG-ADL (A) and QMG (B) in 36 patients from T0 to W24. Bottom: effect of zilucoplan on MGC (C) and MG-QOL-15 (D) in 25 and 16 patients, respectively.
MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite; MG-QOL-15, 15-item Myasthenia Gravis Quality of Life questionnaire; QMG, Myasthenia Gravis quantitative scale; W, weeks. *p < 0.05. **p < 0.001. Error bars show the standard error mean and 95 % CI.

Table 3
Cumulative MG-ADL and QMG responders for patients who completed each time point of follow-up. MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MSE, Minimal symptom expression; QMG, Myasthenia Gravis quantitative scale; ^ MG-ADL responders: patients with reduction in MG-ADL score of at least 3 points from baseline; QMG responders: patients with reduction in QMG score of at least 5 points from baseline.

	Week 1	Week 4	Week 12	Week 24	Week 48
MG-ADL responders ^	19/54	35/54	34/45	29/36	16/18
(%)	(35.2 %)	(64.8 %)	(75.6 %)	(82.9 %)	(88.9 %)
QMG responders ^	7/52	21/54	25/43	24/36	11/18
(%)	(13.0 %)	(39.0 %)	(58.1 %)	(66.7 %)	(57.9 %)
MSE	4/54	9/54	13/45	14/36	10/18
(%)	(7.4 %)	(16.7 %)	(28.9 %)	(38.9 %)	(55.6 %)

3.6. QMG score

A one-way repeated measures ANOVA demonstrated a significant reduction of QMG scores from baseline to W24 (F 17.02, $p < 0.001$, Fig. 1B). The reduction was moderate at the beginning, progressive from week 4 and obtaining a maximum reduction on week 24. QMG reduction was not affected by comorbidities, disease duration, age at disease onset, thymoma, refractoriness, sex and zilucoplan dosage (Supplementary Fig. 8-14).

3.7. QMG responders

QMG responders were defined as patients with reduction in QMG score of at least 5 points from baseline. QMG responder rates were reported between 13.0 at W1 and 66.7 % at W24 (Table 3). Cochran's Q test revealed a significant difference in responder rates across the different timepoints (Q = 32.3, df = 4, $p < 0.001$). Post-hoc analyses using McNemar tests (Bonferroni-corrected $\alpha = 0.0125$) showed a significant difference between W1 and W4 ($p < 0.001$), W1 and W12 ($p < 0.001$), W1 and W24 ($p < 0.001$), but not between W4 and W12 ($p = 0.27$), W4 and W24 ($p = 0.22$), or W12 and W24 ($p = 1.00$).

3.8. MGC score

The analysis was conducted on 25 patients, because many centers did not administer this scale in their routine clinical practice. A one-way repeated measures ANOVA demonstrated a significant reduction of MGC scores from baseline to W24 (F 6.65, $p = 0.001$, Fig. 1C). Comorbidity, disease duration, age at disease onset, thymoma, refractoriness, sex and zilucoplan dosage did not affect the MGC score.

3.9. MG-QoL-15 score

A one-way repeated measures ANOVA demonstrated significant reduction of MG-QoL-15 score from baseline to W24 (F 4.3, $p = 0.022$, Fig. 1D). The effect was not influenced by the presence of comorbidity, disease duration, age at disease onset, thymoma, refractoriness, sex and zilucoplan dosage. The analysis was conducted on 16 patients, as many centers did not use this questionnaire in routine clinical practice.

3.10. Prednisone reduction during follow-up

A one-way repeated measures ANOVA demonstrated a significant reduction of prednisone dosages from baseline to W24 (F 9.86, $p < 0.001$). The reduction observed increased progressively, peaking at week 24 with a mean reduction of -8.38 (1.49) mg of prednisone (Fig. 2A). A faster and more pronounced reduction was obtained in

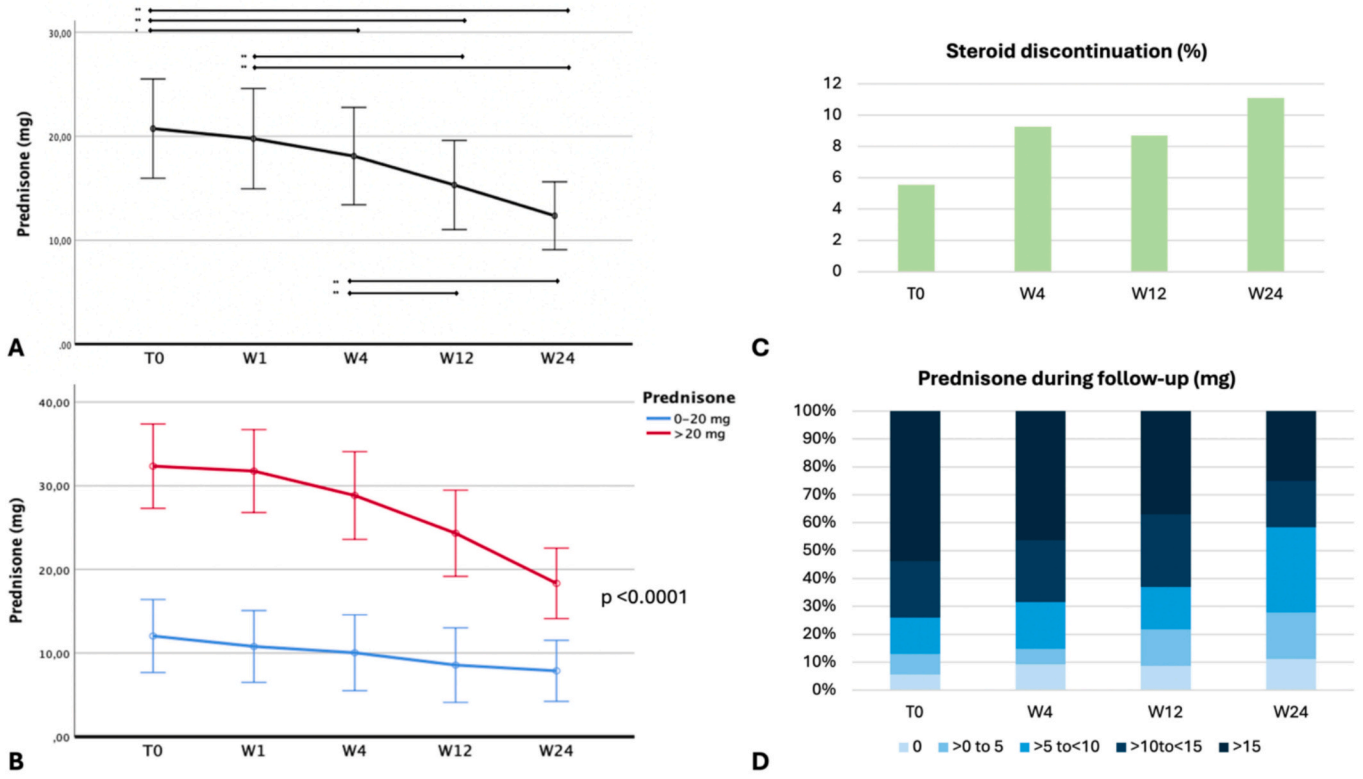

Fig. 2. A: Mean prednisone daily dose (mg) changes during the first 24 weeks of Zilucoplan treatment in patients with anti-AChR gMG. B: mean prednisone daily dose according to prednisone dose showed a more pronounced reduction in patients with prednisone >20 mg at at the start of zilucoplan (red), compared to patients with doses between 0 and 20 mg. C: discontinuation rate of prednisone across time points. D: distribution of prednisone doses during follow-up with zilucoplan. *W*: weeks. *$p < 0.05$. *$p < 0.001$. Error bars show the standard error mean and 95 %CI. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

patients taking more than 20 mg of prednisone at the beginning ($p < 0.001$; Fig. 2B). Moreover, a discontinuation of steroids was achieved in 11 % of patients (Fig. 2C) and most patients significantly reduced the overall intake of steroids across evaluations with more than 50 % of patients under 10 mg at last follow-up available (Fig. 2D). The effect was independent of the presence of comorbidity, disease duration, age at disease onset, thymoma, refractoriness, gender and zilucoplan dose.

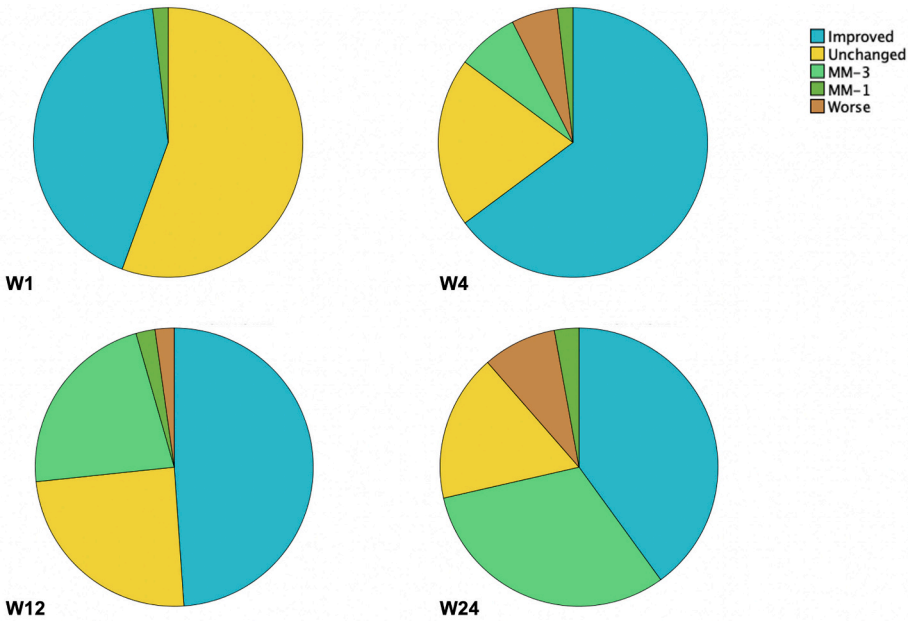

Fig. 3. MGFA-PIS at baseline and each time point. MGFA-PIS, Myasthenia Gravis Foundation of America Post-Intervention Status; MM, minimal-manifestation status; W, weeks.

3.11. MGFA-PIS

After one week of follow-up most patients were stable (30, 55.6 %), 23 patients improved (42.6 %) and a patient was in minimal manifestation status 1 (MM-1, 1.9 %, Fig. 3). At week 4 most patients improved (35, 64.8 %), 11 were stable (20.4 %), 4 in MM-3 (7.4 %) and one in MM-1 (1.9 %). At week 12 most patients improved (22, 40.7 %), 11 remained stable (20.4 %), 10 were in MM-3 (18.5 %), one in MM-1 (1.9 %) and one worsened (1.9 %). At week 24 most patients improved (14, 25.6 %), 11 were in MM-3 (20.4 %), 6 were stable (11.1 %), 3 worsened (5.6 %), and one was in MM-1 (1.9 %).

4. Exacerbations

Forty-seven patients (87.3 %) did not experience exacerbation of MG during the treatment with zilucoplan. The rate of exacerbation was between 0 and 3 events across follow-up. Overall, 7 episodes of exacerbation were reported (12.7 %).

4.1. Rescue therapies

Forty-five patients (83.3 %) needed rescue during the year before starting zilucoplan (Table 1). During the treatment with zilucoplan, a rescue therapy was used in one case at W1 (2.7 %), in 2 patients at W4 (5.5 %), and in 2 patients at W12 (5.5 %). Overall, a rescue therapy was administered in 5 patients (9.3 %) during the observation period.

4.2. Hospitalizations due to MG worsening

Twenty-eight (52 %) patients were hospitalized in the year before zilucoplan. However, 53 patients (98.1 %) did not experience MC during the treatment. Only in one patient (1.9 %) a MC was reported after a week of follow-up. The patient was hospitalized and treated with rescue therapy without discontinuation showing a response to treatment until week 24.

4.3. Adverse events and withdrawals

Zilucoplan subcutaneous self-injection was well tolerated, and most patients did not experience any Aes during follow-up, with good adherence to treatment. There were no severe adverse events (SAEs) after zilucoplan. Mild entity Aes were reported in 16 patients (29 %) during follow-up (Table 4). AEs occurred since W1 and W4, and, in most cases, they were transient and disappeared at the last follow-up. Overall, 8 patients out of 54 (15 %) discontinued the drug due to AEs and further 2 patients due to lack of efficacy (4 %). Survival analysis with Kaplan-Meier method was performed considering follow-up and time of discontinuation (Supplementary Fig. 15). Mantel-Cox test was not significant comparing Kaplan-Meier curves using as factors the presence of comorbidity, disease duration, age at disease onset, thymoma, refractoriness, sex and zilucoplan dose as factors (Supplementary Fig. 16-22).

Table 4
Summary of TEAEs in all patients (n = 54). The variable TEAEs refers to the incidence of TEAEs. TEAEs, treatment-emergent adverse events.

Clinical variable	Total count (N = 54)
No adverse events	38 (70 %)
TEAEs	21 (29 %)
Headache	5 (9 %)
Asymptomatic pancreatic enzyme elevation	3 (6 %)
Abdominal pain	2 (4 %)
Upper respiratory tract infection	2 (4 %)
Nausea	2 (4 %)
Altered mental status	2 (4 %)
Localized scleroderma / Morphea	2 (4 %)
Dizziness	1 (2 %)
Injection site reaction	1 (2 %)
Rash	1 (2 %)

4.4. Predictive factors for response

Univariate analysis showed that chronic IVIg and Zilucoplan dose 23 mg were associated with the MG-ADL response at W12 (Supplementary Table 1); in particular, chronic IVIg increased the chance of a response to W12, while dosage 23 mg was associated with a reduced response. In the multivariate analysis QMG at baseline, 23 mg dosage and chronic IVIg previous treatment were selected, but only the last variable was significantly associated with the outcome chosen (Table 5). Hence, multivariate analysis confirmed the independent association of chronic IVIg alone with MG-ADL response to W12.

5. Discussion

The findings of ZILU25 observational multicenter study confirmed that the complement C5 inhibitor zilucoplan is effective in AchR-positive gMG, with a favourable safety profile. The phase 3 RAISE trial showed that Zilucoplan provided a rapid onset effect compared to placebo, comparable with intravenous C5 inhibition [13]. However, real-world evidence is necessary to confirm the impact of new targeted drugs in the clinical practice, even more when dealing with refractory patients, comorbidities, and other factors that might theoretically impact on the efficacy and safety profiles [9]. In this Italian real-world experience, 54 patients affected by AchR-positive gMG were treated with zilucoplan at 13 Italian referral centers for MG with a mean follow-up of 26 weeks. This cohort of patients was comparable to the RAISE study population in terms of disease duration and age at onset, but with higher mean age, and greater proportion of refractory patients, treatment with NSIST and thymoma [13]. These data confirm the efficacy of zilucoplan in AchR-positive gMG with good safety profile. Indeed, the clinical effect of zilucoplan in gMG was rapid with a statistically significant and clinical meaningful effect since the first week of treatment regarding MG-ADL and QMG scores with maximum effect after 12 weeks and stabilization after 24 weeks of treatment (Fig. 1). Moreover, the entity of the reduction of MG-ADL and QMG scores was comparable with the RAISE study with very similar results on responder analysis for both MG-ADL (76 vs 73 %) and QMG (58 vs 58 %) at W12 [13]. A 2-point change in MG-ADL score and a 3-point change in QMG and in MGC indicate a clinically meaningful improvement, which was obtained in most cases, but in the present study the responder analysis was calculated with a more rigorous criterion of reduction of 3 points on MG-ADL and 5 points on QMG [13]. However, a higher responder rate was reported across time points, reaching 89 % for MG-ADL and 58 % for QMG at W24 (Table 3). Notably, the proportion of patients with MSE at W12 recorded in the ZILU25 study was up to 28.9 %, higher than rates reported in clinical trials (14 % of MSE in the RAISE study and 8-19 % in RAISE-XT at W12) and achieving a further increase to 38.9 % at W24 (compared to 32 % in RAISE-XT at W24) and 56 % at W48 [13,17]. Noteworthy, 4 patients (7.4 %) obtained MSE after only a single week of treatment (Table 3). The high MSE rate might be partially justified by a lower mean MG-ADL score at baseline in this cohort compared to the RAISE study (8.0 in ZILU25 vs 10.9 in ZLP group of RAISE). This difference is likely due to the absence of limitations for MG-ADL scores at baseline for enrolment in the ZILU25 study; however, the indirect effect of zilucoplan cannot be excluded [13].

Prednisone dose consistently lowered over the observation period, starting from W4 to W24, with a reduction of 8.38 mg (40.4 %) at W24. Nevertheless, the steroid dose reduction was not associated with exacerbations, MC, or an increased need for rescue therapies, as demonstrated by a stable and consistent reduction of scores in all clinical scales from W4 to W24 notwithstanding steroid reduction (Table 2, Fig. 1). This confirms a steroid-sparing effect of zilucoplan in AChR-positive gMG, as already reported [17,18] and similarly to those reported with

Table 5
Results of multivariate logistic regression analysis. Baseline refers to the start of zilucoplan. Disease duration was defined as the time between the onset of symptom and the baseline entry. Variables with $p < 0.1$ in univariate analysis were included in multivariate analysis. The bold values represent *p*-values with statistical significance. IVIg, Intravenous immunoglobulins; MG-ADL, Myasthenia Gravis Activity of Daily Living; QMG, Myasthenia Gravis quantitative scale. OR, odds ratio.

Clinical variable	Responders ($N = 34$)	Non-responders ($N = 11$)	p	OR	95 % OR	
					Lower limit	Upper limit
Multivariate						
Chronic IVIg (n, %)	25 (73.5 %)	5 (45.4 %)	**0.048**	5.47	1.01	26.6
Zilucoplan 23 mg	12 (35.3 %)	7 (63.6 %)	0.067	0.21	0.04	1.12
QMG at baseline	14.2 (4.9)	16.7 (4.1)	0.071	0.81	0.64	1.02
MG-ADL at baseline	8.4 (2.7)	8.4 (2.7)	0.26	1.24	0.85	1.81

intravenous complement C5 inhibition [19–21].

The cumulative proportion of patients experiencing exacerbation during treatment was 13 %, and only 9 % required a rescue therapy, with hospitalization in only one case. These data are even more meaningful, considering that 52 % of patients were hospitalized and 83 % had received rescue therapy in the year before treatment (Table 1). Still, longer follow-up data are needed to confirm the reduction of exacerbation and hospitalization with zilucoplan treatment. However, the possibility to receive concomitant IVIg or PLEX during treatment with zilucoplan without needing supplemental dosing, represents a further advantage of zilucoplan treatment in gMG [13].

Finally, zilucoplan improved our patients' quality of life, as shown by the relevant reduction of MG-QOL-15 scores. Indeed, the improvement was progressive from the beginning of treatment, achieving the best results after 12 weeks paralleling the reduction on MG-ADL, QMG and MGC. Of note, zilucoplan is the first subcutaneous C5 inhibitor for gMG [11,12]. Most patients were satisfied with the self-injection route of administration because of increased independence and reduced travelling time to and from hospitals. Furthermore, many patients resumed work, to university, sport activities, and their hobbies.

Zilucoplan subcutaneous self-injection was well tolerated in most patients with good adherence to treatment. TEAEs occurred in 16 (29 %) patients treated with zilucoplan. As already reported in the phase III trial, headache and asymptomatic pancreatic enzyme elevation were commonly reported. Enzyme elevation was transient in all cases, and none led to discontinuation. The incidence of infections was quite low (4 %), and injection site reactions were reported less than expected (2 %) [13]. Of interest, in two patients reported a localized scleroderma, causing discontinuation despite good clinical response. No meningococcal or anaphylactic reactions, or COVID-19 infections occurred. In summary, the profile of zilucoplan was even safer to what was reported in RAISE and RAISE-XT trials, in which the pandemic had partially influenced the results and COVID-19 was among the most common TEAEs [13,17].

This observational study also offers some insights on predictive factors for clinical response and the effects of zilucoplan in MG subtypes. Moreover, efficacy measured on clinical scales was found to be independent from gender, age, age at disease onset, disease duration, thymoma and refractory disease. Furthermore, univariate analysis using as a factor the MG-ADL response at W12 suggested a lower response in patients with higher QMG scores at baseline and in patients treated with zilucoplan 23 mg (Supplementary Table 1). This last result might suggest a risk of undertreatment in patients with particular weight band (56-77 kg), but this was not confirmed by multivariate analysis and this covariate was not significant when comparing the effect on MG-ADL, QMG and MGC on rm-ANOVA. Hence, this result should be considered with caution and should be investigated in larger populations. What is new, patients treated with chronic IVIg treatment seemed to display a better response to zilucoplan; we hypothesized that a higher complement activation as well as a high disease activity in patients chronically treated with IVIg might determine a better response [22–24]. Of interest, the effect of IVIg on complement binding has been demonstrated in vitro, in animal models and in patients treated with IVIg [25]. Moreover, in dermatomyositis IVIg inhibits complement uptake, intercepting the formation and deposition of MAC on the endomysial capillaries [26]. It seems that IVIg might inhibit the uptake of C3b and C4b fragments by sensitized in vitro targets, probably due to formation of covalent or non-covalent complexes between C3 and specific receptor sites within the infused IgG molecules; such an inhibition limits the available C3 molecules for further incorporation into the C5 convertase assembly, thus reducing the activation of the complement cascade [25]. However, this predictive effect of chronic IVIg treatment on the response on complement inhibitors should be investigated and confirmed by future studies.

One of the strengths of ZILU25 study is a wide range of clinician-reported and patient-reported outcomes, showing a consistent effect of zilucoplan in the overall disability and impairments connected to gMG. Unlike clinical trials, in the real-world, there is no obligation to keep fixed CS dosage, hence data on steroid-sparing effect could be collected. Comorbidity data were not reported in the RAISE study, thus allowing a confirmatory data on the impact of them in clinical practice. Also, the multicenter collection of data ensures that the provided results might reflect a real-world Italian clinical setting suitable for improving clinical practice. Limitations are the retrospective design of the study, limited sample size and follow-up. Indeed, some patients discontinued therapy due to lack of symptom control or other concomitant conditions that required treatment discontinuation. The results should be considered preliminary and must be confirmed through larger multicenter studies with standardized outcome measures. Finally, ZILU25 study is ongoing and at the time of publication, some patients had not reached week 24 and 48 and they were not included in the efficacy analysis, reducing the sample for statistical analysis.

In conclusion, Zilucoplan is a new potential treatment option for a broad population of AChR-positive gMG. Zilucoplan was well-tolerated and effective in most patients in any subtypes of AChR-positive gMG with rapid effect onset and sustained benefit across clinical measures. Our study suggests that patients previously treated with chronic IVIg treatment might represent the best candidates for zilucoplan. Further studies with a broader population and longer follow-up are needed to confirm these real-life preliminary data.

Ethical standards statement

All human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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CRediT authorship contribution statement

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Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2025.125671.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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