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C5 complement inhibition versus FcRn modulation in generalised myasthenia gravis

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ABSTRACT

Background Myasthenia gravis (MG) is an autoimmune disorder affecting neuromuscular junctions, leading to fluctuating muscle weakness. While many patients respond well to standard immunosuppression, a substantial subgroup faces ongoing disease activity. Emerging treatments such as complement factor C5 inhibition (C5IT) and neonatal Fc receptor (FcRn) antagonism hold promise for these patients. However, the current landscape is hindered by a paucity of comparative data that is crucial for treatment decisions.

Objective This study aims to compare the effectiveness and safety of C5IT and FcRn antagonists in a real-world setting.

Methods A retrospective analysis of 153 MG patients from 8 German specialised MG centres receiving either C5IT (26 eculizumab, 80 ravulizumab) or efgartigimod (47 patients) was conducted. Propensity score matching (PSM) was employed to compare changes in MG-specific outcome parameters within the first 6 months after treatment initiation, along with safety profiles and concomitant MG therapy.

Results Both treatment strategies led to rapid clinical improvements and substantial reductions in prednisolone doses. However, insufficient response was noted in 20%–49.1% of patients based on Quantitative MG and MG Activities of Daily Living (MG-ADL) scores. We did not identify any new safety concerns. After PSM, 40 patients remained in each group. In both cohorts, reductions in MG-ADL as prespecified primary study endpoint were comparable. Moreover, analyses of secondary outcome parameters demonstrated similar results for C5IT versus FcRn.

Conclusion In contrast to current meta-analyses and indirect comparisons of clinical trial data, our real-world study demonstrates comparable efficacy and safety of C5IT and FcRn antagonism in MG.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Current meta-analyses and indirect comparisons of clinical trial data in generalised myasthenia gravis indicate differences in efficacy and safety between complement and neonatal Fc receptor inhibition.

WHAT THIS STUDY ADDS

⇒ This study provides direct comparisons through a propensity score-matched analysis, demonstrating that both treatment strategies have similar efficacy and safety profiles. Additionally, the study highlights that 20%–50% of patients may experience insufficient treatment responses, emphasising the need for new therapeutic options.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study's findings impact clinical practice by allowing personalised treatment plans based on the comparable efficacy and safety of C5IT and FcRn antagonists. It also highlights the need for new therapies and informed guidelines to address patients who do not respond adequately to existing treatments.

INTRODUCTION

Myasthenia gravis (MG) stands as the most prevalent autoimmune disorder affecting the neuromuscular junction, characterised by antibody-mediated dysfunction of the postsynaptic membrane.[1] Clinically, MG presents with fluctuating weakness affecting ocular, bulbar, respiratory and limb muscles.[2] While standard immunosuppressive treatment (IST) can achieve sufficient symptom control in the majority of MG patients, a significant subgroup encounters a persistent burden of disease and poses an increased risk of myasthenic crises and related morbidity as well as mortality.[2–4] To address these challenges, early fast-acting treatment approaches have been developed with positive long-term effects.[5]

Recent advancements in therapeutic options have provided newfound optimism for this subgroup of patients resistant to conventional treatments. In particular, two therapeutic mechanisms have emerged. Identification of the complement system's pivotal role in driving disease activity in anti-acetylcholine receptor antibody (AChR-ab)[6]

Table 1 BL characteristics of patients treated with complement C5 inhibition (total n=106)

Characteristics	C5IT	Eculizumab	Ravulizumab	P value
Patients, n	106	26	80	
Female patients, n (%)	75 (70.8)	19 (73.1)	56 (70)	>0.999
Age at BL, year, mean (SD)	53.5 (21.2)	50.2 (21.3)	54.6 (21.2)	0.363
Age at diagnosis, year, mean (SD)	45.8 (22.3)	44.5 (22.8)	46.2 (22.3)	0.681
EOMG, n (%)	59 (55.7)	14 (53.9)	45 (56.3)	>0.999
Disease duration, year, mean (SD)	9.7 (9.3)	7.3 (8.3)	10.3 (9.5)	0.124
History of thymectomy, n (%)	64 (60.4)	14 (53.9)	50 (62.5)	0.49
Confirmed thymoma, n (%)	17 (16)	5 (19.2)	12 (15)	0.759
Total number of previous ISTs, mean (min-max)	2.9 (1-8)	2.4 (1-5)	3 (1-8)	0.034
Prednisolone dose at BL, mg/day, mean (SD)	13.5 (17.6)	17.6 (16.6)	12.3 (17)	0.072
Pyridostigmine dose at BL, mg/day, mean (SD)	376 (176.1)	475 (182.4)	330.5 (159.6)	0.0002
QMG score at BL, mean (SD)	12.9 (6.3)	13.4 (5.9)	12.7 (6.4)	0.493
MG-ADL at BL, mean (SD)	8.9 (4.6)	10.4 (5.1)	8.8 (3.9)	0.217
MG-QoL15 at BL, mean (SD)	26.5 (13.7)	32 (13.3)	26.2 (13.8)	0.072
Antibody status				
seropositive, n (%)	106 (100)	26 (100)	80 (100)	>0.999
anti-AChR-Ab, n (%)	106 (100)	26 (100)	80 (100)	>0.999
anti-MuSK-Ab, n (%)	1 (0.9)	0 (0)	1 (1.3)	>0.999
anti-Titin-Ab, n (%)	18 (17)	2 (7.7)	16 (20)	0.23
anti-LRP4-Ab, n (%)	2 (1.9)	0 (0)	2 (2.5)	>0.999
MGFA at BL, n (%)				
I	0 (0)	0 (0)	0 (0)	>0.999
IIA	9 (8.5)	1 (3.9)	8 (10)	0.444
IIB	15 (14.2)	2 (7.7)	13 (16.3)	0.35
IIIA	32 (30.2)	12 (46.2)	20 (25)	0.051
IIIB	31 (29.3)	5 (19.2)	26 (32.5)	0.225
IVA	8 (7.6)	2 (7.7)	6 (7.5)	>0.999
IVB	10 (9.4)	3 (11.5)	7 (8.8)	0.694
V	1 (0.9)	1 (3.9)	0 (0)	0.245

BL is defined as the date of the first infusion of eculizumab (n=26) or ravulizumab (n=80). The disease duration comprises the interval from symptom onset to BL. EOMG is defined by symptom onset prior to the age of 50 years. The right column displays the statistical results of the comparison between eculizumab and ravulizumab. For quantitative variables, two-sided Student's t-test was used as the statistical test. For qualitative variables, Fisher's exact test was employed. A $p<0.05$ was considered statistically significant

Ab, antibody; AChR, acetylcholine receptor; BL, baseline; C5IT, complement factor C5 inhibition therapy; d, days; EOMG, early onset myasthenia gravis; ISTs, immunosuppressive therapies; LRP4, low-density lipoprotein receptor-related protein 4; max, maximum; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15, MG Quality of Life 15-Item Questionnaire; min, minimum; MuSK, muscle-specific tyrosine kinase; n, number; QMG, Quantitaive Myasthenia Gravis.

myasthenia has led to the development of complement C5 inhibitors (C5IT) including eculizumab,[7] ravulizumab[8] and zilucoplan.[9] Additionally, neonatal Fc receptor (FcRn) inhibition, through efgartigimod[10] and rozanolixizumab,[11] has shown promising therapeutic effects. By competing with circulating IgG antibodies for binding the FcRn, these agents interfere with IgG antibody recycling.[10]

While both therapeutic mechanisms have demonstrated substantial reductions in disease severity for many patients, it remains uncertain whether one is superior to the other. A meta-analysis of the randomised, placebo-controlled trials by Saccà *et al* suggested superiority of FcRn antagonists compared with C5IT.[12] However, the interpretability of the trial data is constrained by varying study designs including different inclusion and exclusion criteria. Notably, real-world data comparing these therapies are lacking. Real-world data can provide crucial insights into the actual effectiveness and safety of treatments in less homogeneous cohorts than study populations, reflecting everyday clinical practice outside of the controlled conditions of clinical trials.[13]

Therefore, the objective of this study was to conduct a comprehensive comparison of the new therapeutic mechanisms in MG within a real-world setting. Due to the limited real-world data available for the newly approved medications zilucoplan and rozanolixizumab, this analysis focuses on the complement inhibitors eculizumab and ravulizumab, and the FcRn antagonist efgartigimod.

MATERIAL AND METHODS

Study cohort

Our study comprises a retrospective, observational, multicentric analysis involving patients from eight German university hospitals (Charité Universitätsmedizin Berlin, University Hospital Bochum, University Hospital Düsseldorf, University Hospital Essen, University Hospital Hamburg-Eppendorf, University Hospital Hannover, University Hospital Gießen and University Medical Center Göttingen). MG diagnosis was confirmed based on characteristic clinical manifestations and corroborated by specific antibody results, in line with the national guidelines for MG.[14] Participating centres followed the standardised workflows for MG diagnosis and patient management as defined by the German Myasthenia Gravis Society. Data were collected according to the standards of the German Myasthenia registry and included sociodemographic data, antibody status, MG-specific medication, history of thymectomy, detection of a thymoma, adverse events (AEs), occurrence of myasthenic crises as well as exacerbations and comorbidities. Scoring of MG-specific items was performed by the treating neurologist.

Patient selection

We identified 153 MG patients treated with eculizumab, ravulizumab or efgartigimod between 2018 and 2024. The first eculizumab patient was treated in 2018, the first ravulizumab patient in 2020 and the first efgartigimod patient in 2021.

The following inclusion criteria were applied:

- Confirmed diagnosis of MG in accordance with the national guidelines.[14]
- Age ≥18 years at start of eculizumab, ravulizumab or efgartigimod treatment.

Inclusion criteria for treatment with eculizumab required the presence of anti-AChR-ab-positive MG with a treatment-refractory course, as defined by the criteria for therapy failure outlined in the 'Definitions' section. Efgartigimod was used in

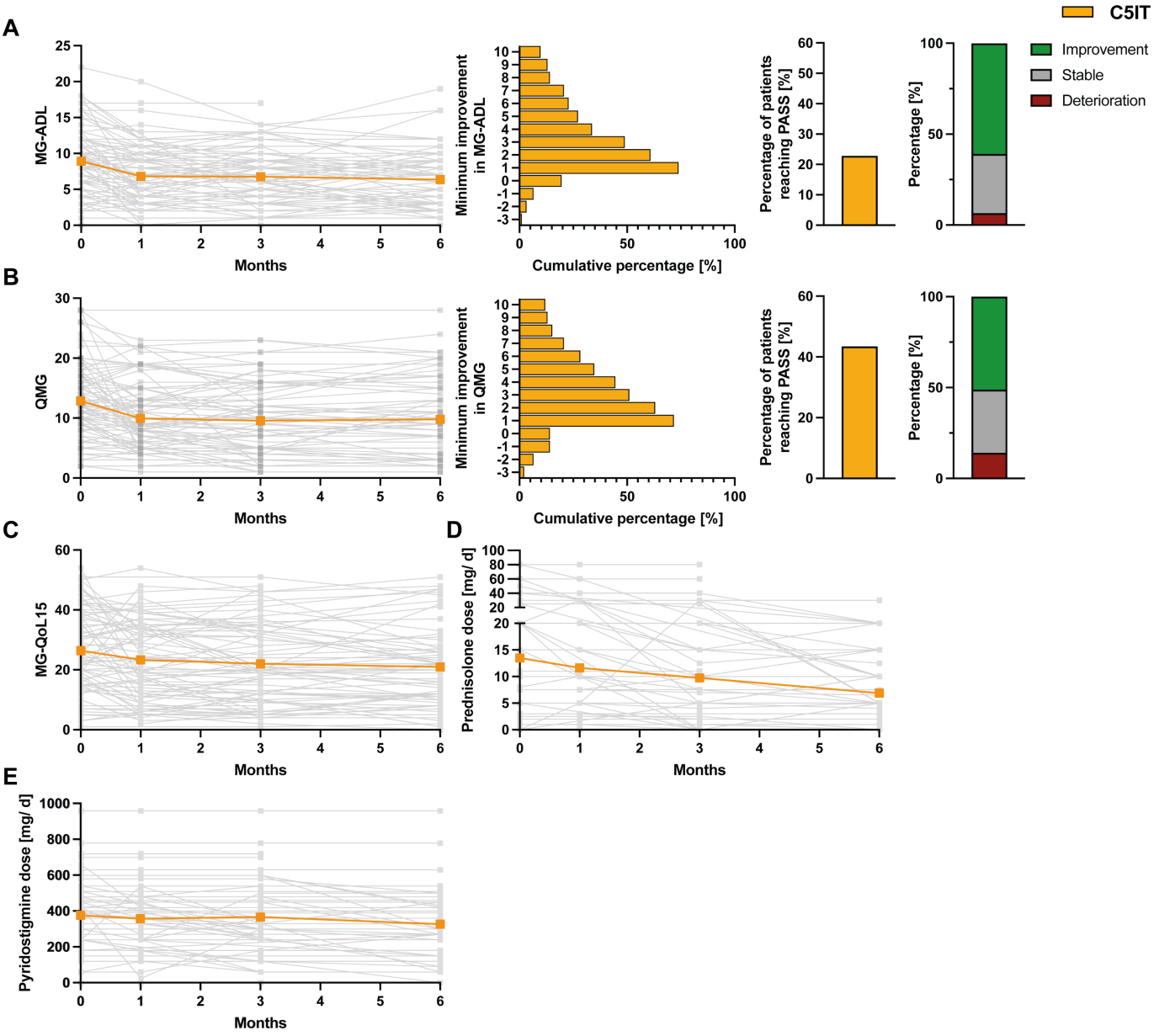

Figure 1 Clinical outcomes in patients receiving C5 complement inhibition therapies. (A) The left panel displays individual changes in MG-ADL scores at months 1, 3 and 6 after BL for patients treated with eculizumab or ravulizumab (grey), along with the mean trajectory (orange). The centre-left diagram illustrates the minimum improvement in MG-ADL based on the best individual response. The centre-right panel shows the proportion of patients achieving PASS as defined by Mendoza *et al*[18] (MG-ADL score ≤2 points). On the right side, the proportion of patients is shown who experienced an MG-ADL deterioration (red), a stable MG-ADL (MG-ADL reduction ≤1 point, grey) or a significant improvement (MG-ADL reduction ≥2 points; green). (B) On the left, individual QMG scores are depicted 1, 3 and 6 months after BL of patients treated with eculizumab or ravulizumab (grey) and for the mean trend (orange). The central-left diagram displays the minimal QMG improvement. On the centre-right, the percentage of patients achieving PASS based on the QMG score is presented (QMG score ≤7). On the right side, the proportion of patients is shown who exhibit a QMG deterioration (red), a stable QMG (QMG reduction of 0–2 points, grey) or a significant improvement (QMG reduction ≥3 points; green). (C–E) Shown are the individual (grey) and the mean courses (orange) for MG-QoL15 (C), dosage of prednisolone (D) and dosage of pyridostigmine (E) in patients undergoing C5IT. BL, baseline; C5IT, complement C5 inhibition therapy; d, day; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL15, Myasthenia Gravis Quality of Life 15-Item Questionnaire; PASS, Patient-acceptable Symptom State; QMG, Quantitative Myasthenia Gravis.

addition to standard therapy for the treatment of adult patients with generalised MG (gMG). Ravulizumab was applied as an add-on therapy to standard treatment of anti-AChR-ab-positive patients with gMG. Standard treatment was defined as the use of corticosteroids, thymectomy, pyridostigmine and, where appropriate, standard IST (including azathioprine, mycophenolate mofetil (MMF), cyclosporine A, methotrexate or tacrolimus).

For the comparison of patients receiving ravulizumab with those treated with efgartigimod, additional inclusion criteria were established:

- Sufficient clinical follow-up data available (baseline (BL) value and at least one follow-up).
- Absence of previous treatment with eculizumab for ravulizumab patients.

Table 2 Safety outcomes in patients treated with complement inhibition

AE	C5IT	Eculizumab	Ravulizumab
Any AE, n (%)	62 (58.5)	14 (53.8)	48 (60)
Headache, n (%)	27 (25.5)	4 (15.4)	23 (28.8)
Total cholinergic AE, n (%)	23 (21.7)	4 (15.4)	19 (23.8)
Upper respiratory tract infection, n (%)	16 (15.1)	1 (3.8)	15 (18.8)
Fatigue, n (%)	16 (15.1)	1 (3.8)	15 (18.8)
Diarrhoea, n (%)	11 (10.4)	3 (11.5)	8 (10)
Nausea, n (%)	10 (9.4)	2 (7.7)	8 (10)
Abdominal pain, n (%)	5 (4.7)	0 (0)	5 (6.3)
Cramps, n (%)	4 (3.8)	0 (0)	4 (5)
Herpes zoster infection, n (%)	4 (3.8)	0 (0)	4 (5)
Nasopharyngitis, n (%)	5 (4.7)	1 (3.8)	4 (5)
Skin rash, n (%)	3 (2.8)	0 (0)	3 (3.8)
Urge symptoms, n (%)	3 (2.8)	0 (0)	3 (3.8)
Urinary tract infection, n (%)	3 (2.8)	0 (0)	3 (3.8)
Arthralgia, n (%)	2 (1.9)	0 (0)	2 (2.5)
Gastrointestinal infection, n (%)	2 (1.9)	0 (0)	2 (2.5)
Hypersalivation, n (%)	2 (1.9)	0 (0)	2 (2.5)
Myalgia, n (%)	2 (1.9)	0 (0)	2 (2.5)
Renal impairment, n (%)	2 (1.9)	0 (0)	2 (2.5)
Shivering, n (%)	3 (2.8)	1 (3.8)	2 (2.5)
Myasthenic exacerbations, n (%)	22 (20.8)	9 (34.6)	13 (16.3)
Myasthenic crisis, n (%)	8 (7.5)	4 (15.4)	4 (5)
Hospitalisation due to exacerbation/ crisis, n	21	8	13
Duration of hospitalisation, day, mean	11.6	11.7	11.6
Rescue therapy			
IA, n	2	1	1
IVIG, n	13	7	6
PLEX, n	5	1	4
No therapy, n	13	5	8
Trigger			
Infectious, n	20	8	12
Vaccination, n	2	2	0
Unknown, n	8	3	5
Any SAE other than myasthenic crisis, n (%)	5 (4.7)	0 (0)	5 (6.3)
Asystolia, n	1 (0.9)	0 (0)	1 (1.3)
Arm fracture, n	1 (0.9)	0 (0)	1 (1.3)
Gastrointestinal infection leading to hospitalisation, n	1 (0.9)	0 (0)	1 (1.3)
Hip fracture, n	1 (0.9)	0 (0)	1 (1.3)
Heart failure, n	1 (0.9)	0 (0)	1 (1.3)
Pancreatitis, n	1 (0.9)	0 (0)	1 (1.3)
Thrombosis, n	1 (0.9)	0 (0)	1 (1.3)
Upper respiratory tract infection leading to hospitalisation, n	2 (1.9)	0 (0)	2 (2.5)
Deaths, n (%)	1 (0.9)	0 (0)	1 (1.3)
Withdrawals (%)	19 (17.9)	9 (34.6)	10 (12.5)
Limited effectiveness	15	5	10
Change of C5 inhibition	4	4	0

Listed are AEs that occurred at least twice and all SAEs for the total complement inhibition cohort as well as for eculizumab (n=26) or ravulizumab (n=80) subgroups.
AE, adverse event; C5, complement factor C5; IA, immune adsorption; IVIG, intravenous immunoglobulins; n, number; PLEX, plasma exchange; SAE, serious AE.

Dosing regimen

All treatments were performed in accordance with the summary of product characteristics for the individual agent and are detailed in the online supplemental methods.

Definitions

An age of 50 years at disease onset was used as cut-off point between early-onset (<50 years) and late-onset (≥50 years) MG (LOMG).[15] A decrease of ≥2 points in the MG Activities of Daily Living (ADL) and a decrease of ≥3 points in the Quantitative MG (QMG) score were defined as criteria for the responder analysis.[10] An early response was defined as a clinically significant improvement (MG-ADL reduction ≥2 points, QMG improvement ≥3 points) observed by the 3-month follow-up. For the analysis of early and late responders, only patients with clinical scores available for all time points were included. The definitions for myasthenic exacerbations or crises were based on the criteria outlined in the national guidelines.[14] Minimal symptom expression (MSE) was defined as an MG-ADL score ≤1. Therapy refractoriness was defined as a persistent impairment in activities of daily living despite treatment with ≥2 immunosuppressive therapies (as monotherapy or in combination) including corticosteroids over a year or failure of ≥1 immunosuppressive therapy, requiring regular plasma exchange or intravenous immunoglobulins every 3 months for the past year.

Study outcomes

Primary outcome parameter was the maximum reduction in MG-ADL scores.[16] MG-ADL scores were collected at BL (prior to treatment initiation) as well as 1 (14–45 days post-BL), 3 (60–120 days post-BL) and 6 months after BL (150–210 days post-BL). Furthermore, secondary analyses were carried out on the trends in the pyridostigmine and prednisolone dosage as well as the QMG[17] and MG Quality of Life 15 (MG-QoL-15) scores. Given the varying regimens of the treatments under investigation, analyses were performed using the best individual response for each case. For the analysis of the PASS (Patient Acceptable Symptom State), the following thresholds, as defined by Mendoza *et al*, were used: MG-ADL score ≤2, QMG score ≤7 points.[18] Study outcomes were prespecified before data analysis.

Statistical analysis

Statistical analysis was performed by using RStudio V.1.4.1103 (R-Tools Technology) and Prism V.10 (GraphPad Software). Continuous data are presented as mean (±SEM). Differences between groups were analysed using a two-tailed, unpaired t-test for quantitative variables and two-tailed Fisher's exact test for categorical variables. For comparison of the best individual response with BL scores, a paired t-test was applied.

A propensity score matching (PSM) was used to account for imbalances of treatment cohorts at BL. We used a fixed 1:1 matching using the nearest-suitable neighbour method without replacement. Propensity scores were calculated using a logistic regression model including 'sex', 'use of concomitant IST', 'LOMG status, 'age at BL', 'detection of thymoma', 'steroid dose at BL', 'MG-ADL at BL' and 'QMG at BL'. The sufficiency of PSM was evaluated by comparing standardised mean differences of BL characteristics among respective cohorts. To estimate the treatment effect and its SE, we fit a linear regression model with the maximum reduction of the MG-ADL as the primary outcome parameter and the treatment, covariates and their interaction as predictors and included the full matching weights in the estimation.

Differences were considered statistically significant with the following p values: *p<0.05, **p<0.01, ***p<0.001.

RESULTS

Complement inhibition

In total, 106 patients undergoing C5IT were included in the study. The BL characteristics of patients receiving C5IT are presented in table 1. As observed in phase 3 trials,[7 8] rapid

Table 3 BL characteristics of patients treated with FcRn inhibition (total n=47)

Characteristics	FcRn inhibition
Patients, n	47
Female patients, n (%)	31 (66)
Age at BL, year, mean (SD)	53 (16.5)
Age at diagnosis, year, mean (SD)	47.9 (16.9)
EOMG, n (%)	24 (51.1)
Disease duration, year, mean (SD)	7.2 (9.6)
History of thymectomy, n (%)	30 (63.8)
Confirmed thymoma, n (%)	8 (17)
Total number of previous ISTs, mean (min-max)	1.9 (0–4)
Prednisolone dose at BL, mg/day, mean (SD)	13.7 (14.7)
Pyridostigmine dose at BL, mg/day, mean (SD)	403.3 (161)
QMG score at BL, mean (SD)	12.1 (7.2)
MG-ADL at BL, mean (SD)	9.4 (4.4)
MG-QoL15 at BL, mean (SD)	32.4 (10.7)
Antibody status	
Seronegative, n (%)	4 (8.5)
Seropositive, n (%)	43 (91.5)
Anti-AChR-Ab, n (%)	43 (91.5)
Anti-Titin-Ab, n (%)	6 (12.8)
Anti-LRP4-Ab, n (%)	2 (4.3)
Anti-MuSK-Ab, n (%)	0 (0)
MGFA at BL, n (%)	
I	0 (0)
IIA	4 (8.5)
IIB	5 (10.6)
IIIA	17 (36.2)
IIIB	16 (34)
IVA	0 (0)
IVB	4 (8.5)
V	1 (2.1)
Interval duration, week, mean (SD)	5.8 (2.9)
Number of cycles, mean (SD)	4 (1.8)

BL refers to the first infusion of efgartigimod. Disease duration was defined as the time between symptom onset and BL. EOMG is characterised by the occurrence of first MG symptoms before the age of 50.
Ab, antibody; AChR, acetylcholine receptor; BL, baseline; EOMG, early onset myasthenia gravis; FcRn, neonatal Fc receptor; ISTs, immunosuppressive therapies; LRP4, low-density lipoprotein receptor-related protein 4; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15, MG Quality of Life 15-Item Questionnaire; n, number; QMG, Quantitative Myasthenia gravis.

improvements in MG-ADL (month 1: −2.1±2.9 compared with BL) and QMG scores (month 1: −2.9±4.1) were noted under complement inhibition, with stable courses over the following 5 months (MG-ADL: −2.6±3.9; QMG: −3.1±5.1 after 6 months compared with BL) (figure 1A, B). Clinically meaningful responses, defined as an improvement of at least two points in MG-ADL or a reduction of three points in QMG, were observed in 65 (61.3%) and 54 (50.9%) of patients, respectively. Based on the best individual MG-ADL response, seven (6.6%) patients experienced a clinical deterioration. Given that steroid reductions were only observed in patients without an increase in MG-ADL score, it seems unlikely that insufficient steroid dosage was the underlying cause of symptom worsening. Regarding the QMG, 15 (14.2%) patients had a worsening of symptoms, and 37 (34.9%) had a stable clinical course. These improvements resulted in 24 (22.6%) of patients meeting the PASS threshold based on the MG-ADL (MG-ADL ≤2 points), and 46 (43.4%) according to the QMG score (QMG ≤7 points). In 12 (11.3%) patients MSE was observed. Mean MG-QoL15 scores improved by 5.5±11.7 points after 6 months (figure 1C). The mean dose of prednisolone declined by about half, from 13.5±17.6 mg/day to 6.9±7.1 mg/day after 6 months (figure 1D) and the mean pyridostigmine dose was reduced by 49.7±98.2 mg/day (figure 1E). Comparing BL values with the best individual response, there was a significant difference for MG-ADL (8.9±4.6 vs 5.6±3.7; p<0.0001), QMG (12.9±6.3 vs 8.8±5.8; p<0.0001), MG-QoL15 (26.5±13.7 vs 19.36±13.1; p<0.0001), prednisolone doses (13.5±17.6 vs 5.3±12.13 mg/day; p=0.0001) and pyridostigmine doses (376±176.1 vs 318.5±190.1 mg/day; p<0.0001).

AEs were reported by 62 (58.5%) of patients, with the most common being headaches (27 (25.5%)), upper respiratory tract infections (16 (15.1%)) and fatigue (16 (15.1%)) (table 2). During the second administration of ravulizumab, one patient (0.9%) experienced asystolia requiring resuscitation. However, the patient passed away for unknown reasons 52 days after the fourth administration. Overall, 22 (20.8%) patients experienced a myasthenic exacerbation, and 8 (7.5%) had a crisis with an average onset of 351.1±483.7 days after BL. None of these patients died. The causes of exacerbations and crises were predominantly related to infections (66.7%). A total of 19 (17.9%) patients discontinued therapy, including 15 (14.2%) due to lack of efficacy and four (3.7%) due to switching from eculizumab to ravulizumab.

Dividing the C5IT cohort into those treated with eculizumab (n=26) and ravulizumab (n=80), we found higher number of previous ISTs (3 vs 2.4; p=0.034) in patients treated with ravulizumab. Additionally, initial doses of pyridostigmine (475±182.4 vs 330.5±159.9 mg/day; p=0.0002) were lower in ravulizumab patients. Other BL characteristics were comparable (table 1).

In terms of the clinical outcome, changes in QMG and MG-ADL scores were comparable (QMG: −5.4±4.9 (eculizumab) vs −3±4.3 (ravulizumab), p=0.252; MG-ADL: −4.4±4.1 vs −2.6±4.2, p=0.401) as shown in online supplemental figures 1 and 2. The proportion of patients who experienced a worsening, stable or improved course was also similar. The same applies to the MG-QoL15 score and the reduction of MG concomitant medication. Comparing BL values with the best individual response, there were significant improvements in both cohorts for MG-ADL (eculizumab: 10.4±5.1 vs 5.3±4.4, p<0.0001; ravulizumab: 8.8±3.9 vs 4.9±3.8; p<0.0001), the QMG (eculizumab: 13.4±5.9 vs 7.6±4.9, p<0.0001; ravulizumab: 12.7±6.4 vs 8.8±4.6, p<0.0001), the MG-QoL15 score (eculizumab: 32±13.3 vs 19.9±12.4, p=0.0003; ravulizumab: 26.2±13.8 vs 17.5±13.4 p<0.0001), daily prednisolone dose (eculizumab: 17.6±16.6 vs 10.3±12.6 mg/day, p=0.0039; ravulizumab: 12.3±17 vs 5.9±8.6 mg/day, p=0.0003) and pyridostigmine dose (eculizumab: 475±182.4 vs 391.9±233.9 mg/day, p=0.0097; ravulizumab: 330.5±159.6 vs 245.2±172.1 mg/day, p<0.0001).

For the safety profile, we found no significant differences. Of note, there was a trend of more frequent myasthenic exacerbations (9 (34.6%) vs 13 patients (16.3%); p=0.056) as well as crises (4 (15.4%) vs 4 patients (5%); p=0.099) in the eculizumab group (table 2). Given the generally later occurrence of these exacerbations and crises in the eculizumab cohort (498.4±605.7 vs 203.8±271.3 days after BL; p=0.123), this could be explained by a longer follow-up period.

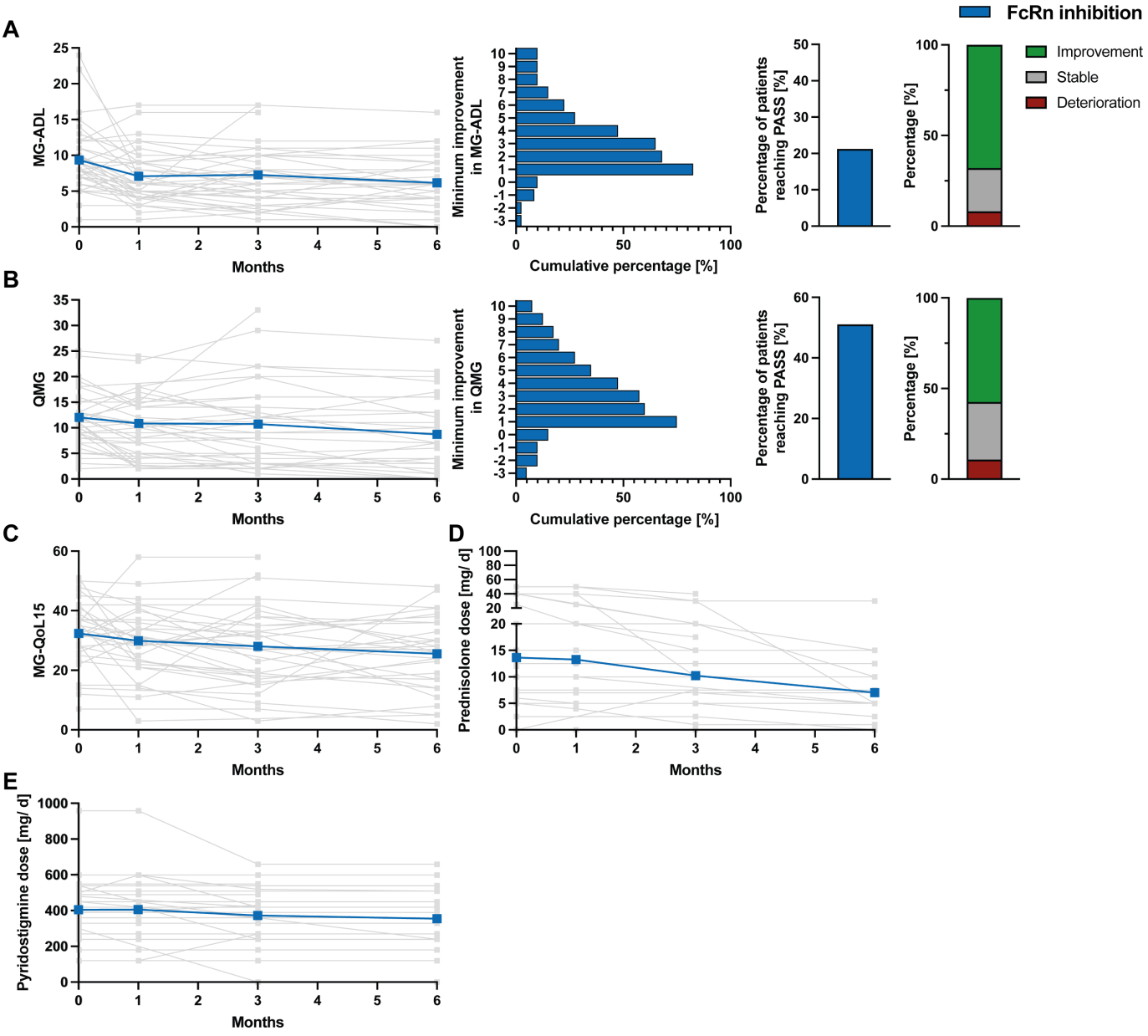

Figure 2 Clinical outcome parameters of patients treated with efgartigimod. (A) In the left panel, the MG-ADL scores of patients at months 1, 3 and 6 after initiation of FcRn inhibition therapy are individually shown in grey, with the group's average trajectory displayed in blue. The diagram in the centre-left shows the cumulative percentage of the minimal improvement in MG-ADL scores. On the centre-right, the proportion of patients meeting the PASS criteria established by Mendoza *et al*[18] is indicated (MG-ADL score ≤2). On the right side, the proportion of patients is shown who experienced an MG-ADL deterioration (red), a stable MG-ADL (MG-ADL reduction of 0–1 points, grey) or a significant improvement (MG-ADL reduction ≥2 points; green). (B) On the left, individual QMG scores (grey) and the overall trajectory (blue) are depicted for the first 6 months after BL in patients treated with efgartigimod. The diagram in the middle-left shows the cumulative percentage of the minimum QMG improvement. The centre-right panel indicates the proportion of patients achieving a PASS based on the best individual response (QMG score ≤7). On the right side, the proportion of patients is shown who exhibit a QMG deterioration (red), a stable QMG (QMG reduction of 0–2 points, grey) or a significant improvement (QMG reduction ≥3 points; green). (C–E) The individual trajectories (grey) and mean courses (blue) for patients treated with FcRn inhibition are presented concerning MG-QoL15 (C), doses of prednisolone (D) as well as of pyridostigmine (E). BL, baseline; d, day; FcRn, neonatal Fc receptor; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL15, MG Quality of Life 15-Item Questionnaire; PASS, Patient-acceptable Symptom State; QMG, Quantitative Myasthenia Gravis.

FcRn inhibition

The cohort of patients treated with efgartigimod comprised 47 patients (table 3). Notably, based on the results of the phase 3 study,[10] four seronegative patients (8.5%) were treated with efgartigimod. Compared with complement inhibition, patients receiving FcRn inhibition had a significantly higher MG-QoL15 at BL (32.4±10.7 vs 26.5±13.7; p=0.0233).

After 6 months, MG-ADL scores decreased from 9.4±4.4 to 6.2±3.6 (figure 2A). QMG reduction showed a discrete temporal latency (month 1: −1.2±3.7 compared with BL, month 6: −3.3±5.4) (figure 2B). PASS was achieved by ten (21.3%) patients in terms of the MG-ADL and 24 (51.1%) based on the QMG, while 5 (10.6%) patients met MSE criteria. Four (8.5%) and five (10.6%) patients experienced worsening in terms of

Table 4 Safety outcomes in patients treated with efgartigimod

AE	FcRn inhibition
Any AE, n (%)	27 (57.4)
Upper respiratory tract infection, n (%)	11 (23.4)
Headache, n (%)	5 (10.6)
Fatigue, n (%)	4 (8.5)
Nasopharyngitis, n (%)	4 (8.5)
Nausea, n (%)	3 (6.4)
Urinary tract infection, n (%)	3 (6.4)
Myasthenic exacerbations, n (%)	11 (23.4)
Myasthenic crisis, n (%)	5 (10.6)
Hospitalisation due to exacerbation/crisis, n	13
Duration of hospitalisation, day, mean	12.6
Rescue therapy	
IA, n	2
IVIG, n	8
PLEX, n	6
No therapy, n	5
Trigger	
Infectious, n	7
Pancreatitis, n	2
Drug-induced, n	1
Unknown, n	6
Any SAE other than myasthenic crisis, n (%)	0 (0)
Deaths, n (%)	0 (0)
Withdrawals (%)	4 (8.5)
Limited effectiveness	4
Due to AEs	1

Presented are AEs occurring at least twice as well as all serious AEs observed under therapy with efgartigimod.
AE, adverse event; FcRn, neonatal Fc receptor; IA, immune adsorption; IVIG, intravenous immunoglobulins; n, number; PLEX, plasma exchange; SAE, serious AE.

MG-ADL and QMG scores, respectively. As steroid reductions were only noted in patients who did not experience an increase in the MG-ADL score, it is unlikely that symptom worsening was the consequence of lowered steroid doses.

Responder rates were 32 (68.1%) patients for the MG-ADL and 27 (57.4%) for the QMG score. The MG-QoL15 decreased by 6.8±11.4 points after 6 months (figure 2C). Substantial reductions were also achieved in the daily doses of prednisolone (−6.6±11.6 mg/day) (figure 2D) and pyridostigmine (−49.6±133.4 mg/day) (figure 2E). No significant differences in response were found between the four seronegative and the seropositive patients (online supplemental figure 3). Comparing BL values with the best individual response, there was a significant difference for MG-ADL (9.4±4.4 vs 5.6±3.7; p<0.0001), QMG (12.1±7.2 vs 8±7.3; p<0.0001), the MG-QoL15 score (32.4±10.7 vs 22.8±12.33; p<0.0001), the prednisolone (13.7±14.7 vs 6.4±8.3 mg/day; p=0.006) and the pyridostigmine dose (403.3±161 vs 344±155.7 mg/day; p=0.0046).

AEs occurred in 27 (57.4%) of patients (table 4). Myasthenic exacerbations under efgartigimod treatment were reported in 11 (23.4%) and crises in five (10.6%) patients with a mean occurrence 160.3±108.7 days after therapy initiation. Of note, there was one patient (2.1%) experiencing three crises and one exacerbation. Two myasthenic crises were triggered by pancreatitis that occurred under treatment with MMF. The other causes were predominantly infectious or remained unclear. Four (8.5%) patients discontinued therapy, all due to limited efficacy and one additionally due to AEs.

In view of the importance of response timing, an analysis was also conducted to assess the temporal response of symptoms. Patients who showed a clinically significant improvement by the 3-month time point were classified as early responders, while those who responded at the 6-month follow-up were categorised as late responders.[19] No significant differences were observed between the groups (online supplemental figure 4).

Comparison of both treatment mechanisms

Finally, a direct comparison of both treatment modalities was conducted, considering only patients with sufficient follow-up data. Given different labels and varying approval times for eculizumab compared with efgartigimod and ravulizumab, the comparison of the therapeutic mechanisms focused on ravulizumab and efgartigimod. Of note, patients who had previously received eculizumab were excluded from the ravulizumab group, as these patients had already established complement inhibition prior to initiation of ravulizumab. To account for pretreatment disease severity and reduce selection bias, a model of PSM was employed. Covariates considered were sex, age at baseline, thymoma status, steroid dosage at BL, use of concomitant immunosuppression, LOMG status, MG-ADL and QMG scores at BL (online supplemental figure 5). 40 patients per group were included in the final analysis (figure 3).

There were no significant differences in the BL characteristics despite a higher MG-QoL15 score in the efgartigimod group (ravulizumab: 24.4±13.3 vs efgartigimod: 32.1±11.4, p=0.01) (online supplemental table 1).

Given the different forms of therapy intervals, a comparison of both groups was primarily based on the maximum reduction in MG-ADL scores considering the best individual response. In total, MG-ADL scores were available for 100% of the included patients at BL, 93% after 1 month, 94% after 3 months and 89% after 6 months. Regarding the QMG, scores were available for 100% at BL, 91% after 1 month, 94% after 3 months and 88% after 6 months. A reduction of 4.7±3.7 or 4.3±4.2 points in the MG-ADL score was found under ravulizumab or efgartigimod, respectively (p=0.637; figure 4A). The maximum QMG reduction was 5.4±7.1 under ravulizumab and 5.8±5.4 under FcRn inhibition (p=0.76; figure 4B). Regarding the MG-ADL, no relevant differences were observed at any time point (BL: ravulizumab 9.6±4 vs efgartigimod 9.2±4.6; month 1: 6.9±4 vs 6.3±3.8; month 3: 6.7±3.7 vs 6.5±4; month 6: 5.9±3.8 vs 6.1±4.5). Concerning the QMG score, the ravulizumab group showed an average score of 12.2±6.4 at BL, 9.5±5.6 after 1 month, 8.8±5.7 after 3 months and 8.1±5.9 after 6 months. In the efgartigimod group, the QMG scores were 11.9±7 at BL, 8.8±6.9 after 1 month, 9.2±8.7 after 3 months and 8.5±8.8 after 6 months. Comparable numbers of patients in both groups met PASS criteria based on MG-ADL (ravulizumab 11 (27.5%) vs efgartigimod 10 (25%) patients; p>0.999) as well as QMG (ravulizumab: 20 (50%) vs efgartigimod: 22 (55%) patients; p=0.823) and MSE (ravulizumab: 6 (15%) vs efgartigimod: 5 (12.5%) patients; p>0.999). Regarding MG-ADL, 32 (80%) of the patients receiving ravulizumab and 28 (70%) of the patients treated with efgartigimod were considered treatment-responders (p=0.439), and for QMG, 25 (62.5%) or 27 (67.5%) patients, respectively (p=0.815). For the MG-QoL15, we found a maximum decrease of 8.1±9.8 (ravulizumab) and 9.4±9.5 (efgartigimod) (p=0.572; figure 4C). Reductions in daily prednisolone (5.3±8.2 vs 6.7±11.5 mg/day; p=0.525) and pyridostigmine doses (56.6±115.4 vs 37.4±74.4 mg/day; p=0.401) were comparable (figure 4D,E).

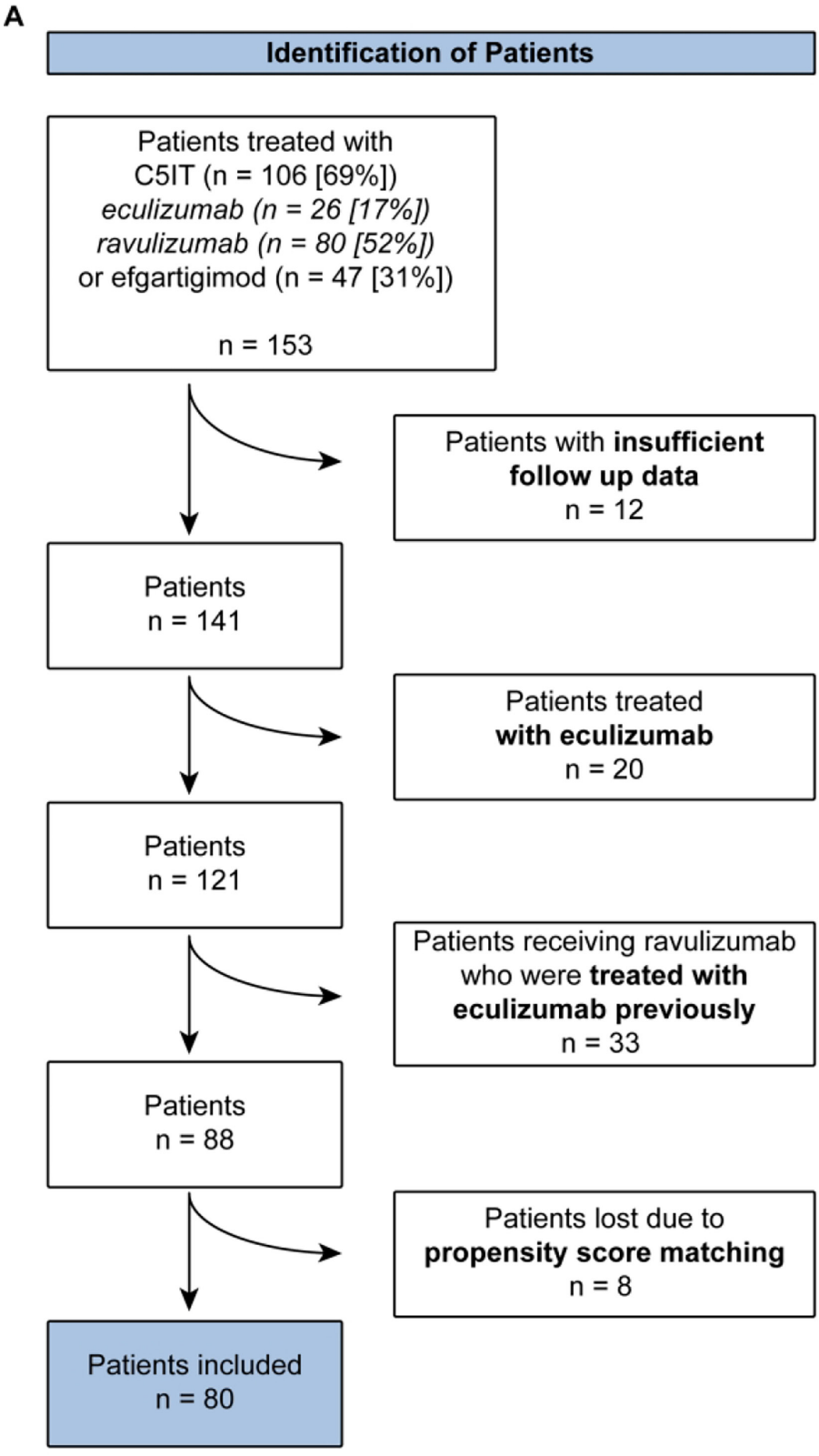

Figure 3 Flow chart detailing patient inclusion. 80 patients were included for the final comparison. C5IT, complement C5 inhibition therapy.

Regarding the safety profile, there were no significant differences except for an increased occurrence of cholinergic side effects in the ravulizumab group (9 (22.5%) vs 0 (0%); p=0.0024) (online supplemental table 2). In seven (17.5%) patients treated with ravulizumab and eight (20%) under efgartigimod, myasthenic exacerbations were reported, while myasthenic crises were observed in two patients receiving ravulizumab and five under FcRn antagonisms. Myasthenic exacerbations and crises occurred 184.5±213 days after initiation of ravulizumab and 153.3±119.9 days after BL in efgartigimod patients (p=0.693).

Finally, a comparison of efgartigimod versus C5IT receiving patients including both eculizumab and ravulizumab was

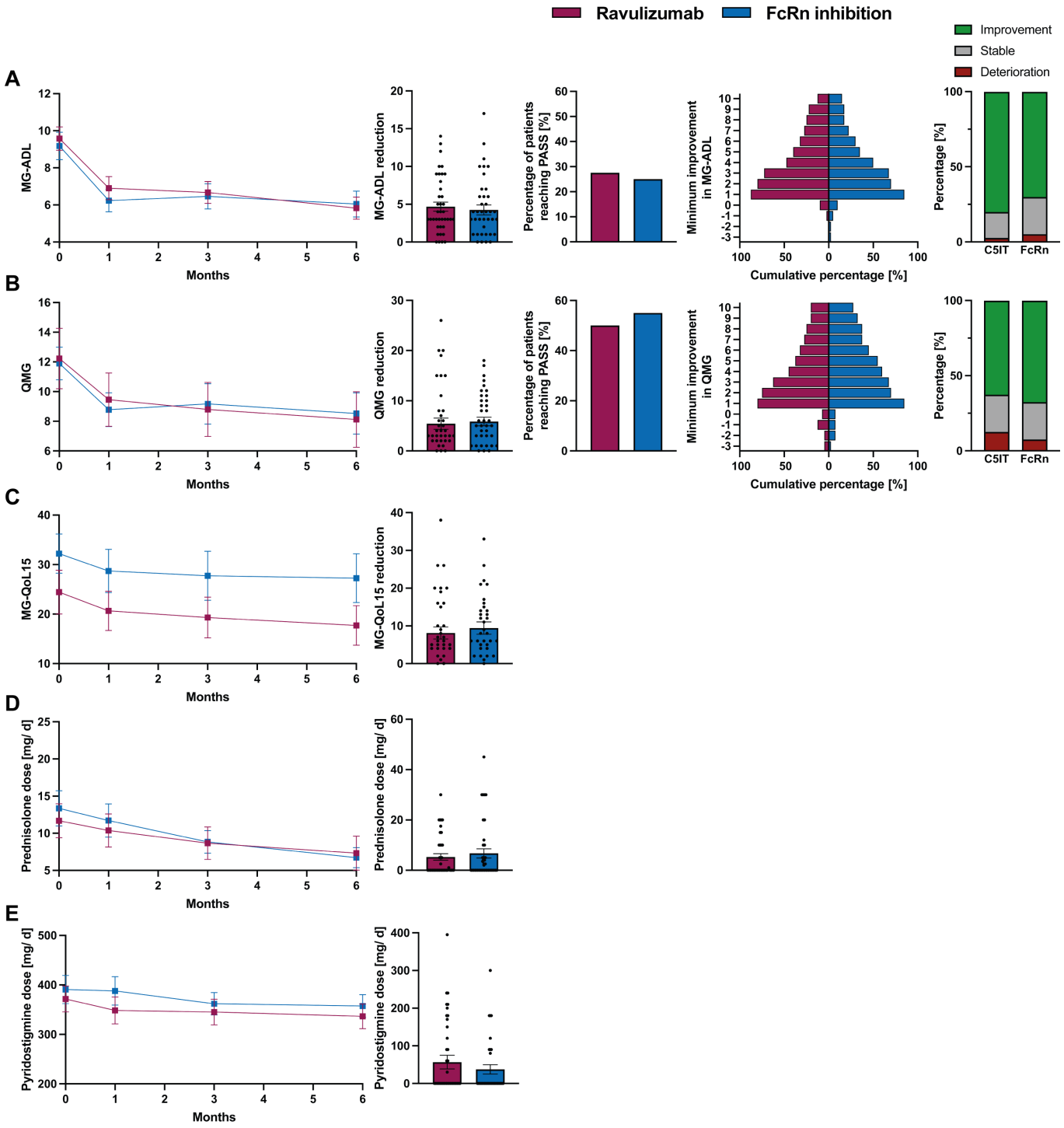

Figure 4 Comparison of clinical outcome parameters in patients treated with ravulizumab or efgartigimod. Clinical outcome measures for patients receiving add-on treatment with ravulizumab (red) or efgartigimod (blue) were examined. Cohort comparability was established through propensity score matching considering sex, age at treatment initiation, use of concomitant immunosuppressive therapy, thymoma status, LOMG status, steroid dosage at BL, MG-ADL scores at BL and QMG scores at BL. (A) presents the mean MG-ADL scores after 1, 3 and 6 months (left), the maximal reduction in MG-ADL score (centre-left), the proportion of patients achieving PASS based on the MG-ADL score (MG-ADL ≤2 points; centre) and minimal improvements in MG-ADL score (centre-right). The right diagram depicts the proportion who experienced an MG-ADL deterioration (red), a stable MG-ADL (reduction of 0–1 points, grey) or a relevant improvement (MG-ADL reduction ≥2 points; green). (B) illustrates the average QMG scores at months 1, 3 and 6 post-BL (left), the maximum decrease in QMG score (centre-left), the percentage of patients meeting PASS criteria based on the QMG score (QMG ≤7 points; centre) and the minimum improvement in total QMG scores (centre-right). The right graph shows the proportion of patients with a QMG deterioration (red), a stable QMG (QMG reduction of 0–2 points, grey) or a significant improvement (QMG reduction ≥3 points; green). (C–E) Left panels show the mean course and the right diagrams the maximal reductions in MG-QoL15 scores (C), daily prednisolone (D) as well as pyridostigmine doses (E). Error bars represent the mean with 95% CI. Quantitative variables were analysed using a two-sided Student's t-test. A $p<0.05$ was considered statistically significant. BL, baseline; d, day; FcRn, neonatal Fc receptor; MG-ADL, Myasthenia Gravis Activities of Daily Living; LOMG, late-onset Myasthenia Gravis; MG-QoL15, MG Quality of Life 15-Item Questionnaire; PASS, Patient-acceptable Symptom State; QMG, Quantitative Myasthenia Gravis.

conducted after PSM (online supplemental figure 6). To overcome the limitations of different approvals, only patients who met the Eculizumab label criteria regarding treatment refractoriness were considered. A total of 39 patients were included per group. Again, we found no significant differences (online supplemental figure 7, online supplemental table 3, 4).

Thus, both treatment strategies demonstrated comparable efficacy and safety outcomes.

DISCUSSION

In this study, we present the largest real-world data to date on the new therapeutic agents for the treatment of MG and conducted a comparative analysis of these therapies regarding their efficacy and safety. Our results indicate that both therapeutic mechanisms provide similar clinical benefits, reducing symptom burden and disease severity, also benefiting previously treatment-refractory patients. However, depending on the used outcome parameter around 20%–50% of patients demonstrated insufficient responses.

Comparing our data on eculizumab to the phase-3 REGAIN-trial, we observed a higher proportion of MG-ADL treatment responders in our cohort (82% vs 60%) with similar results for mean reductions in MG-ADL, QMG and MG-QoL15. In the open-label extension (OLE) of the REGAIN trial, 29 of 117 (24.8%) patients reported exacerbations, including three (2.6%) cases with with myasthenic crises.[20] Compared with this, in our cohort, nine (34.6%) patients experienced a myasthenic exacerbation and four (15.4%) suffered a crisis, which may be related to differences in BL characteristics such as age at treatment initiation and a slightly higher proportion of females. Our findings on eculizumab efficacy are supported by further real-world studies from the USA and Japan.[21–23]

Regarding ravulizumab, the phase 3 CHAMPION trial demonstrated an MG-ADL reduction of 3.1 and QMG improvement of 2.8 points after 26 weeks.[8] In our cohort, we observed similar effects, with reductions of 2.6 and 3 points, respectively. The proportion of MG-ADL (decrease by ≥3 points) and QMG responders (decrease by ≥5 points) was comparable for MG-ADL and more pronounced for QMG (35.5% vs 54.4%) in our cohort. Eight Patients (9%) experienced clinical deterioration, including one myasthenic crisis. In contrast, in our cohort, 13 patients (16.3%) experienced a myasthenic exacerbation, and four patients (5%) had a myasthenic crisis.

For efgartigimod, our cohort demonstrated similar effectiveness compared with the phase 3 ADAPT trial following the initial cycle, with responder rates of 68% vs 70% for MG-ADL and 63% vs 57.4% for the QMG score.[10] The responder rates in the OLE were higher after more cycles, compared with our results, which might indicate a delayed clinical response to efgartigimod as supported by our data. Again, we observed higher rates of exacerbations (11 patients (23.4%)) and crises (five patients (10.6%)) than in the ADAPT trial (one exacerbation meeting SAE criteria). Considering overall existing real-world data on the efficacy of efgartigimod, there are slight variations in reported outcomes.[24–28] Absolute reductions in MG-ADL ranged from 3.6 to 6.5 points after multiple cycles of treatment. Our reported MG-ADL reduction of 3.2 points is slightly below the range observed in other real-world studies potentially related to different patient cohorts and varying follow-up durations. Reported responder rates varied between 62% and 86.3%.[24–28]

Existing meta-analyses are based on data from the respective randomised controlled trials. Of note, they provided heterogeneous results either favouring FcRn or C5IT, despite employing a similar approach.[12 29 30] A recent study using a matching-adjusted indirect comparison for efgartigimod and ravulizumab indicated a significantly better outcome for the revised MG-QoL15 after 26 weeks in the efgartigimod group, as well as for MG-ADL and QMG after 4 weeks, with a faster achievement of the best response for all mentioned parameters.[31] In contrast, our data suggest a slightly delayed response to efgartigimod. Overall, our analysis based on PSM-matched real-world cohorts does not support the reported differences in clinical efficacy and safety for FcRn or C5IT in MG. These conflicting results may be related to natural limitations of such indirect comparisons based on phase II and III studies including differing inclusion criteria, study population characteristics and varying study designs.

Nonetheless, this study is potentially subject to inherent biases and limitations. Patients from eight different German specialised MG centres were included in the study, yet we found no clear indication of a centre bias (data not shown). Moreover, potential bias may arise from the exclusive enrolment of patients from tertiary MG centres. However, myasthenia patients receiving those new therapies are primarily treated at tertiary centres, thus reflecting the majority of current patient care. In addition, BL characteristics concerning age, disease duration and MG-specific treatment are similar to those of another large MG study in Germany.[32] Another limitation may involve the collection of clinical data at the time points of 1, 3 and 6 months after BL, which may not have captured the best responses for every patient, particularly given the fluctuations in myasthenic symptoms, especially under FcRn antagonism. To address this drawback, we chose the best individual response for each patient over the entire observation period as the primary endpoint to depict the potentially optimal treatment outcome.

It is also important to note that a range of ±1 month was established for the follow-up assessments after 3 and 6 months. This approach was necessary due to the interindividual variability in disease progression and treatment response, which required individualised follow-up schedules, and because the retrospective nature of the study did not allow for predetermined follow-up visits. To ensure a representative dataset for balanced analysis, we established this scheme, although it may naturally introduce some bias. However, considering that the therapies under investigation typically reach their maximum effect after 4–8 weeks, we believe that the potential impact on the analysis is likely to be limited.

From our analyses, it also becomes evident that a relevant proportion of around 20%–49.1% of patients still shows insufficient response to these new treatment strategies with higher rates of myasthenic crises than reported in clinical trials. Therefore, some patients may require other treatment strategies such as B and/or T cell depletion/modulation incl. CAR-T cell aproaches.[33]

Overall, our real-world study suggests that both C5IT and FcRn inhibition provide significant clinical benefits in terms of symptom reduction and quality of life improvement, with neither therapy showing superior efficacy nor safety. To further elucidate the comparative effectiveness and safety profiles of these therapies, the acquisition of prospective data is crucial. The aim of these studies should also be to identify predictive factors for the response to C5IT or FcRn antagonism.

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Contributors NH, LG, AM and TR designed the study and methods. Formal analysis was done by NH and TR. Clinical data were by provided NH, LG, MH, CN, FS, SH, MÖ, CBS, SL, MS, CS, CS-G, SP, HHK, FFK, TS, MP, SG, JZ, VS, AT, TH, SGM, AM and TR. Resources were provided by AM and TR. NH and TR wrote the original draft. LG, MH, CN, FS, SH, MÖ, CBS, SL, MS, CS, CS-G, SP, HHK, FFK, TS, MP, SG, JZ, VS, AT, TH, SGM and AM reviewed and edited the manuscript. Figures were created by NH and TR. Supervision by AM and TR. Guarantor of the study: TR.

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Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and all patients gave informed consent in the framework of the German Myasthenia registry (https://dmg.online/myasthenie-register). The study was registered at the WHO-licensed German clinical trial registry (DRKS00024099). The study was approved by the ethics committee of the Charité-Universitätsmedizin Berlin (EA1/025/11). For Hannover, patients were included under a separate ethics approval (9741_BO_S_2021). Participants gave informed consent to participate in the study before taking part.

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