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Symptomatic treatment of myasthenia gravis and its role in the era of emerging immunomodulatory treatments

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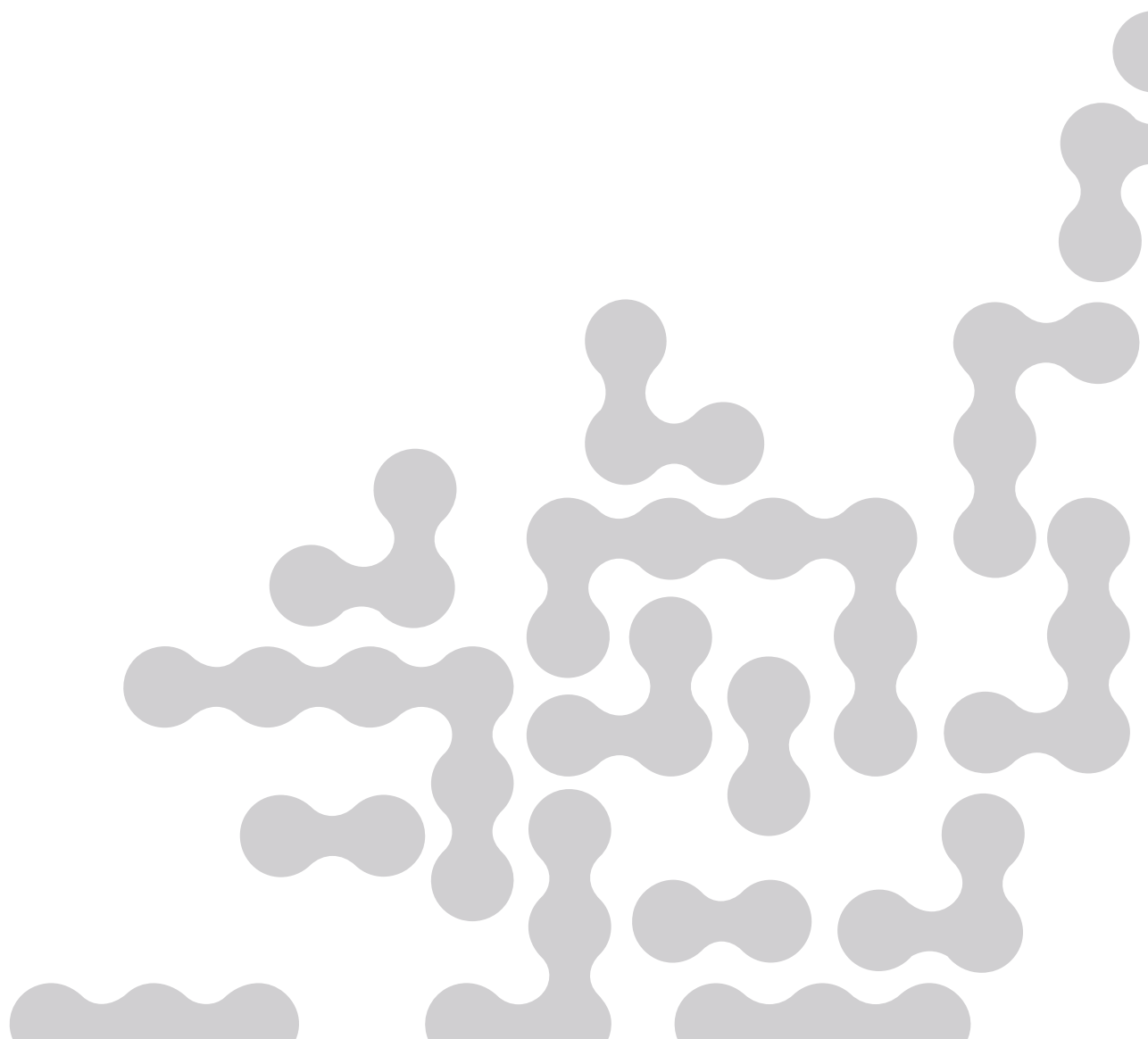
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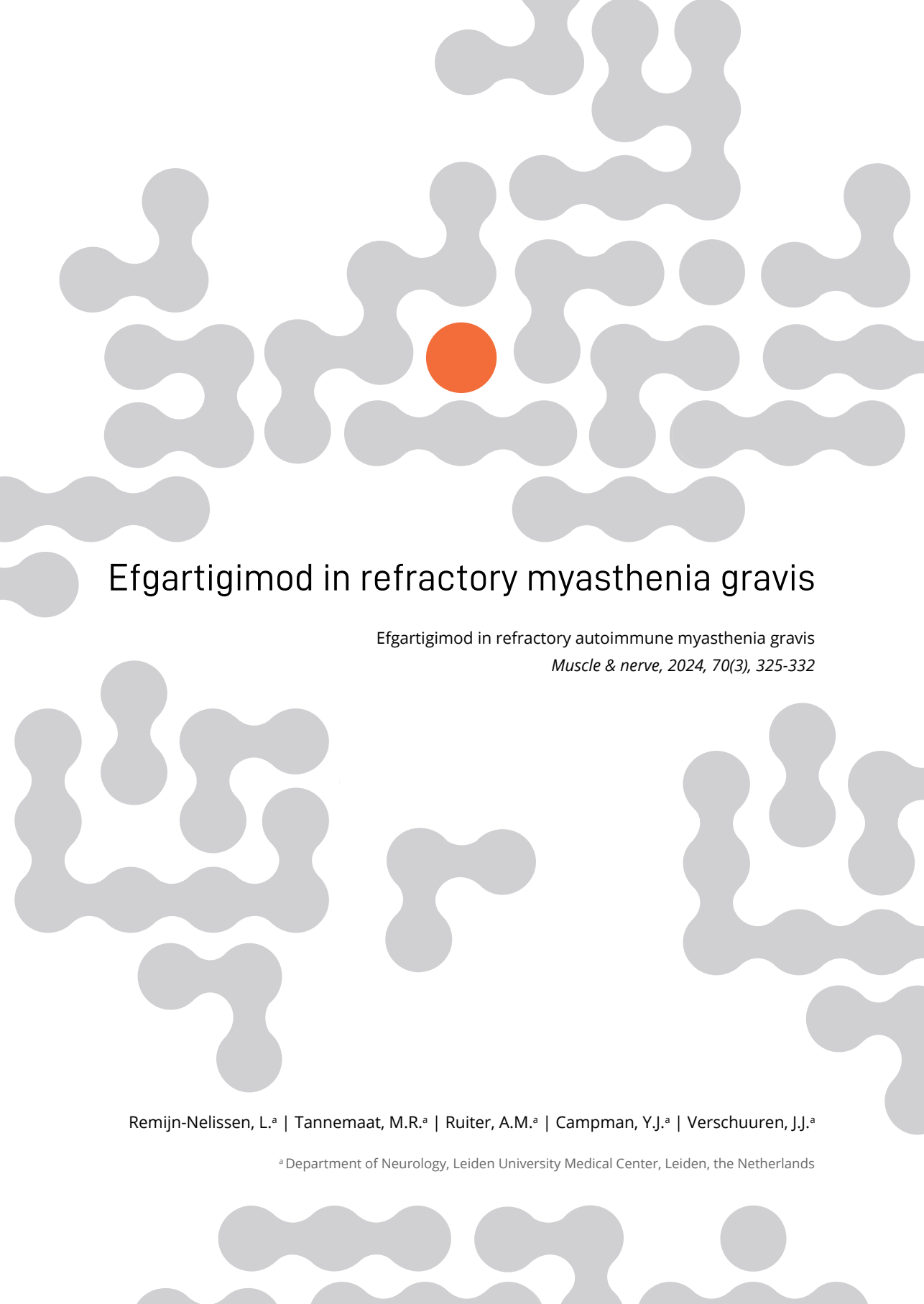
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CHAPTER

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Efgartigimod in refractory myasthenia gravis

Efgartigimod in refractory autoimmune myasthenia gravis
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Abstract

Introduction/Aims

Efgartigimod, a neonatal Fc-receptor inhibitor, has recently been approved as treatment for myasthenia gravis (MG). In this retrospective cohort study, we aimed to systematically assess short- and long-term effectiveness of efgartigimod in patients with refractory MG.

Methods

Sixteen patients with refractory autoimmune acetylcholine receptor MG were treated with efgartigimod. Data were collected from January 2021 to March 2023 on Myasthenia Gravis Activities of Daily Living (MG-ADL), Quantitative Myasthenia Gravis score (QMG), Myasthenia Gravis Composite score (MGC) and the 15-item revised version of the Myasthenia Gravis Quality of Life questionnaire (MG-QoL15r).

Results

A favorable outcome was seen in 56% of patients at the last measurement. Out of 16 patients, 50% were an MG-ADL responder after the first treatment cycle. After four weeks, a clinically meaningful improvement compared to baseline was seen on the MG-ADL, QMG, and MGC. There was a statistically significant improvement on the MGQoL15r from baseline to week 4. The improvement was maintained until the last measurement for the MGC and the MGQoL15r. At the last visit, all patients had discontinued 4-weekly dosages, shifting to administration frequencies of one, two, or three weeks. Drug doses could be decreased for prednisolone (n=7), azathioprine (n=2) and intravenous immunoglobulins (n=9). Frequency of plasma exchange was decreased in nine patients.

Discussion

In patients with refractory MG, efgartigimod was effective for at least half of all patients. Patients required more frequent dosing compared to the ADAPT phase 3 trial. In 80% of the patients concurrent medication could be reduced or ceased.

Introduction

In recent years, the neonatal Fc receptor has become an important target for new therapies in several antibody-mediated autoimmune diseases, including myasthenia gravis (MG).^{185,186} In 2021, the efficacy and tolerability of intravenous efgartigimod, a neonatal Fc receptor antagonist, was demonstrated in patients with generalized MG.⁶² Efgartigimod was effective in improving muscle strength and overall disease status in patients with generalized MG. Treatment was generally well-tolerated, with the most common adverse events being mild to moderate in nature. Interim results of the ADAPT+ have shown the long-term efficacy and safety of efgartigimod in generalized MG.¹⁸⁷ However, its effectiveness in patients with refractory MG has not been established. Although there are various definitions of refractory MG,^{25,57,129,188,189} it is estimated that in approximately 10 percent of patients with generalized MG, conventional therapies are not sufficient.¹⁹⁰ Patients with refractory MG are generally excluded from clinical trials due to the requirement of intensive treatment with multiple drugs, chronic IVIg or plasma exchange and frequent adjustments in the dosing of their medical treatment.

Following approval by the European Medicines Agency, an expanded access program (EAP) was initiated to provide treatment with efgartigimod to patients prior to marketing authorization. In this study, we present the results of long-term treatment with efgartigimod in a cohort of patients with refractory MG.

Methods

Patients

In this retrospective cohort study, all patients with MG in whom treatment with efgartigimod was initiated between January 2021 and March 2023 as part of the EAP, were included. Patients were treated at the department of neurology at Leiden University Medical Center, a tertiary center for the treatment of MG in the Netherlands. As efgartigimod at the time of treatment was not a registered drug in the Netherlands, efgartigimod was provided by argenx (Ghent, Belgium) on a named patient basis. A named patient program is a regulatory mechanism enabling individual patient access to investigational drugs for serious medical conditions outside of clinical trials, with strict oversight from the supervisory authority responsible for monitoring the quality and safety of healthcare and youth care services in the Netherlands, the Health and Youth Care Inspectorate. All requests for access to efgartigimod were unsolicited. Apart from providing efgartigimod for use, argenx was not involved in any clinical decision, nor did the manufacturer contribute to the process of data collection and data analysis. The eligibility criteria for approval for the EAP were: clinical

criteria of MGFA class II, III, IVa, or IVb; patient's screening Myasthenia Gravis Activities of Daily Living (MG-ADL)-score of at least 5, with at least 50% of the total score attributed to non-ocular symptoms; treatment with pyridostigmine for at least 4 weeks; treatment with prednisolone for at least 6 weeks; treatment for at least 3 months with at least one of the following: azathioprine, mycophenolate mofetil, cyclosporine, or methotrexate. If medication had to be discontinued due to side effects, minimum treatment periods did not apply as a restriction.

Moreover, we required all patients to have refractory MG, as defined by 1) unsatisfactory functioning due to either persistent MG symptoms or side effects of current treatments, without clinical evidence of other significant serious diseases 2) treatment with two or more immunosuppressive therapies for 12 months without symptom control OR at least one immunosuppressive therapy with intravenous immunoglobulin or plasma exchange given at least four times per year⁶. The decision whether or not to treat a patient with efgartigimod was made as part of clinical care through collaborative consultation between the treating physician and the patient.

Treatment

Efgartigimod was administered intravenously at a dose of 10 mg/kg with one infusion per week during four weeks. All efgartigimod administrations were given in the hospital. After four weeks the dosing frequency was adjusted based on clinical symptoms, IgG level and side effects at the discretion of the treating physician. All participating patients were evaluated weekly up to 4 weeks. Thereafter outcome measures were recorded at each hospital visit. The decision to initiate rescue treatment was at the treating physician's discretion.

Outcome measures

All measurements conducted were performed within the scope of routine clinical care. In order to fully optimize and understand the clinical effect of this novel drug on patients within the EAP, we established a standardized evaluation protocol, consisting of QMG, MG-ADL, MGC and the 15-item revised version of the Myasthenia Gravis Quality of Life questionnaire (MG-QoL15r) before each administration of efgartigimod. Measurements were conducted by a trained nurse practitioner. A clinically meaningful improvement was defined as an improvement of ≥ 2 points (MG-ADL) or ≥ 3 points (QMG + MGC) from baseline¹¹. A responder was defined as a patient who had an improvement of ≥ 2 points (MG-ADL) or ≥ 3 points (QMG + MGC) at 4 weeks, sustained for at least 4 consecutive weeks. In cases where patient data was not available at 8 weeks, the closest available value was used. Demographic and clinical data (age, sex, medical history, clinical phenotype of MG, laboratory tests including IgG levels and acetylcholine receptor (AChR) antibody titers), comorbidities and concomitant medications or procedures were retrospectively collected. Chronic

intravenous immunoglobulin therapy (IVIg) or chronic plasma exchange was defined as treatment given periodically (at predetermined fixed intervals) or any patient who had received ≥ 4 treatment cycles in the previous year. To establish baseline IgG values, we obtained the most recent IgG level before the introduction of efgartigimod that was unaffected by plasma exchange or IVIg. IgG levels determined within 28 days after administration of IVIg¹² and within 6 weeks after plasma exchange¹³ were excluded in all analyses. The semi-quantitative determination of AChR antibodies in serum was performed in the context of clinical practice by using a standard dilution of the sample in a radioimmunoassay (RSR Limited, Cardiff, UK). This assay provides a numerical value that is linearly correlated with actual serum concentrations up to a value of 20 nmol/L. A favorable outcome was defined as: 1) a clinically meaningful improvement on at least two outcome measures (MG-ADL, QMG or MGC) or 2) discontinuation of prednisolone or a prednisolone dose reduction of >10 mg per day or 3) discontinuation of chronic plasma exchange or IVIg, and 4) no use of rescue medication.

All data were gathered in the process of routine clinical care and a formal medical ethical approval was therefore not required for this particular study according to Dutch law. All patients provided written informed consent for the collection and analysis of these data.

Statistical analyses

Sample size calculations were not performed given the descriptive nature of this study. Demographic and clinical data at baseline were evaluated using descriptive statistics. A Kaplan-Meier plot was generated to illustrate efgartigimod persistence over time. For the analysis of clinical effectiveness, the mean change from baseline for each outcome measure (MG-ADL, QMG, MGC, MG-QoL15r) was evaluated. Analyses of change from baseline for each visit were performed using the paired t-test. Missing values were not imputed. All statistical analyses were performed with IBM SPSS Statistics (version 25.0). All graphs were made with GraphPad Prism software (version 9.3.1 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com).

Results

Baseline characteristics

Efgartigimod was evaluated in sixteen patients. Median follow-up time was 29.5 (IQR 10-50.5) weeks. Demographics and clinical characteristics at baseline are summarized in **Table 7.1**. All patients met the criteria of refractory MG. At baseline, before the initiation of efgartigimod, four patients were treated with chronic IVIg, and five patients with chronic plasma exchange.

Treatment characteristics

A total of 309 efgartigimod infusions were provided until data cutoff. Treatment characteristics are summarized in **Table 7.2**.

At the last visit, none of the patients were still undergoing treatment in cycles of 4-weekly dosages. All patients switched to a one, two or three weekly frequency of administrations (**Figure 7.1**).

Table 7.1 Baseline characteristics

	All patients (n=16)
Age (years) , mean (SD)	47.3 (16.8)
Sex	
Male	5 (31%)
Female	11 (69%)
Myasthenia gravis duration (years) , median (IQR)	12 (4-17)
Previous thymectomy	12 (75%)
Previous thymoma	6 (38%)
Immunomodulatory treatments at baseline	
Corticosteroids	11 (75%)
Any NSIST	11 (75%)
Intravenous immunoglobulin therapy	
≤4 weeks before efgartigimod initiation	4 (25%)
Multiple treatments in the preceding year	9 (56%)
Plasma exchange	
≤6 weeks before efgartigimod initiation	7 (44%)
Multiple treatments in the preceding year	9 (56%)
No treatment [§]	1 (6%)
History of immunomodulatory treatments	
Corticosteroids	16 (100%)
NSIST	
1	3 (19%)
2	7 (44%)
≥3	6 (38%)
Intravenous immunoglobulin therapy	15 (94%)
Plasma exchange	14 (88%)
Outcome measures, mean (SD)	
MG-ADL	7.9 (4.5)
QMG	14.1 (7.0)
MGC	13.1 (6.9)
MG-QoL15r	17.8 (7.5)

Data are n (%) unless otherwise specified. Abbreviations: NSIST, non-steroidal immunosuppressant therapy.[§] Patient declined to take any medication.

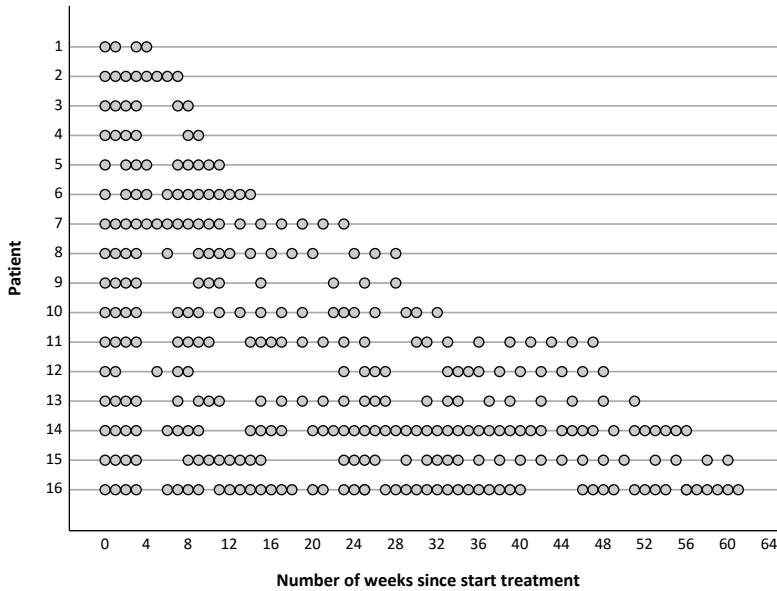


Figure 7.1 Efgartigimod administrations since treatment start for each individual patient

Clinical effectiveness

Data of 16 patients, were evaluated at 4 weeks after start of the treatment. At 4 weeks, one patient had received 2 infusions of efgartigimod, all other patients received 4 infusions. Eight (50%) were an MG-ADL responder (**Table 7.3**). Nine patients fulfilled our criteria for a favorable outcome (56.3%) (**Table 7.2**).

Four patients continued the use of efgartigimod, although they did not fulfill the criteria for a favorable outcome. For three patients, the decision to continue efgartigimod was based on the observed subjective clinical improvement by the patient and the clinician.

A clinically meaningful improvement compared to baseline was seen on the MG-ADL (mean -4.37 points, 95% CI [-2.39 to -6.36], $p < 0.001$), QMG (mean -4.93 points, 95% CI [-2.42 to -7.45], $p < 0.001$), and MGC (mean -7.60 points, 95% CI [-4.48 to -10.72], $p < 0.001$). The MGQoL15r showed a statistically significant improvement between baseline and week 4 (mean -5.75 points, 95% CI [-2.16 to -9.35], $p = 0.005$) (**Figure 7.2**).

The last measurement was performed at a median of 28 weeks (IQR 9-52) for the MG-ADL, 16 weeks (IQR 5-28) for the QMG, 20 weeks (IQR 8-48) for the MGC and 24 weeks (IQR 14-33) for the MG-QoL15r. The improvement was sustained until the last measurement for the MGC (mean -3.31 points, 95% CI [-0.39 to -6.24], $p = 0.029$ and the MGQoL15r (mean -4.71

points, 95% CI [-1.62 to -7.81], $p=0.006$), but not for the MG-ADL (mean -2.31 points, 95% CI [0.15 to -4.78], $p=0.064$) and QMG (mean -2.25 points, 95% CI [0.39 to -4.89], $p=0.089$). All four patients who discontinued treatment with efgartigimod, stopped within the first hundred days of treatment (**Figure 7.3**). Out of these four patients, three patients discontinued because of lack of efficacy. One patient declined further treatment with efgartigimod for reasons not further specified. Rescue medication was used in five patients (**Table 7.2**) and consisted of plasma exchange ($n=5$), intravenous immunoglobulins ($n=1$), prednisolone ($n=3$), (re)start of non-steroidal immunosuppressant drugs such as azathioprine ($n=1$), mycophenolate mofetil ($n=1$), rituximab ($n=2$) and eculizumab ($n=2$). Median time until the first rescue medication was 56 days (IQR 24-126 days).

One patient did not use any medication at the initiation of efgartigimod. Out of the other 15 patients, 12 (80%) were able to reduce any medication. In seven patients, the dose of prednisolone could be lowered (**Figure 7.4A**). The median decrease in prednisolone dose was 5 mg (IQR 0 to 20 mg). Out of six patients, three patients were able to lower the dose of azathioprine (**Figure 7.4B**). In all thirteen patients treated with IVIg or plasma exchange, either as needed or chronically, in the period before the initiation of efgartigimod, the number of IVIg doses (**Figure 7.4C**) and plasma exchanges (**Figure 7.4D**) was lower after the initiation of efgartigimod.

Table 7.2 Efgartigimod treatment characteristics

	All patients (n=16)
Favorable outcome	9 (56%)
Discontinued treatment	4 (25%)
Treatment duration (days), median (IQR)	208 (78-352)
Number of doses, median (IQR)	17 (9-25)
Lowest IgG level achieved, mean (SD)	3.4 (± 1.3)
Max. IgG change vs. baseline [#] (%), mean (SD)	64.8 (± 13.8)
Rescue medication	5 (31%)

Data are n (%) unless otherwise specified. [#]Missing values, $n=7$

Table 7.3 Summary of outcome measures

	MG-ADL	QMG	MGC
Clinically meaningful improvement			
4 weeks	10/16 (63%)	9/15 (60%)	11/15 (73%)
Last measurement	7/16 (44%)	8/15 (53%)	8/15 (53%)
Responder	8/16 (50%)	6/11 (55%)	5/10 (50%)

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite score; QMG, Quantitative Myasthenia Gravis score

IgG levels and AChR antibody titers

In 9 patients, changes in IgG levels from baseline were analyzed (Table 7.2). Figure 7.5 shows serum IgG levels and AChR antibody titers for each patient during treatment with efgartigimod. Despite frequent dosing, the lowest IgG level achieved stayed above 2.0 g/L in 15 out of 16 patients. In only one patient, an IgG level of 1.7 g/L was seen, which returned to levels above 2.0 g/L after the discontinuation of efgartigimod. Patients who empirically ended up with a treatment schedule with weekly administrations demonstrated a consistently higher AChR antibody titer throughout the entire treatment period compared to patients who were in need of treatment every two or three weeks.

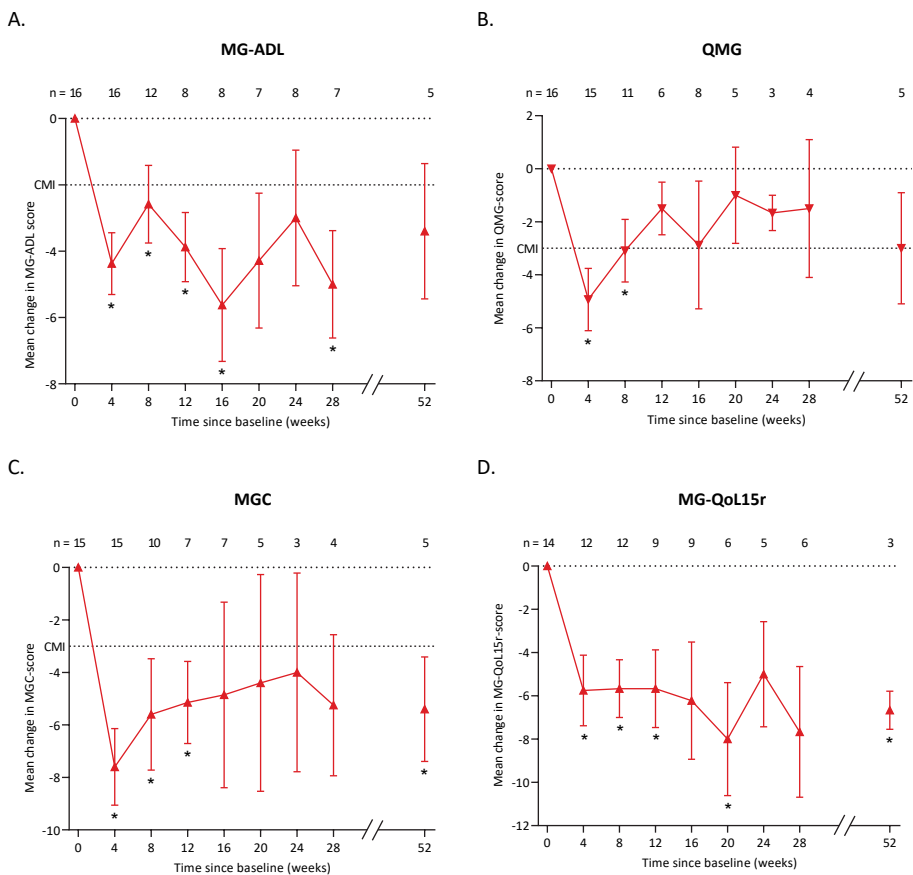


Figure 7.2 Mean change in Myasthenia Gravis Activities of Daily Living (A), Quantitative Myasthenia Gravis score (B), Myasthenia Gravis Composite score (C), and 15-item revised version of the Myasthenia Gravis Quality of Life questionnaire (D) during 28 weeks and at 52 weeks

During the first four weeks efgartigimod was administered weekly, after these four weeks the dosing frequency was adjusted at the discretion of the treating physician. *Indicates a statistically significant change from baseline ($P < 0.05$). Error bars show standard error. CMI; clinically meaningful improvement.¹⁹¹

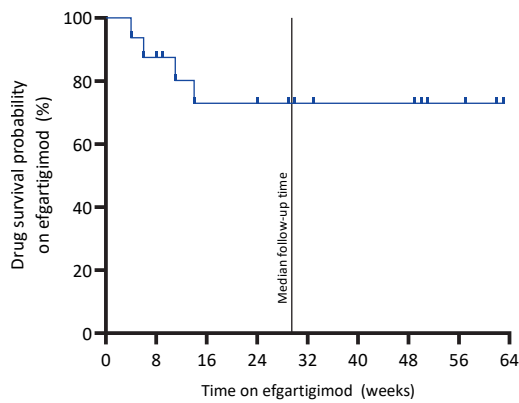


Figure 7.3 Kaplan-Meier curve illustrating efgartigimod persistence in 16 patients with refractory myasthenia gravis
Median follow-up time 29.5 weeks (interquartile range 10-50.5).

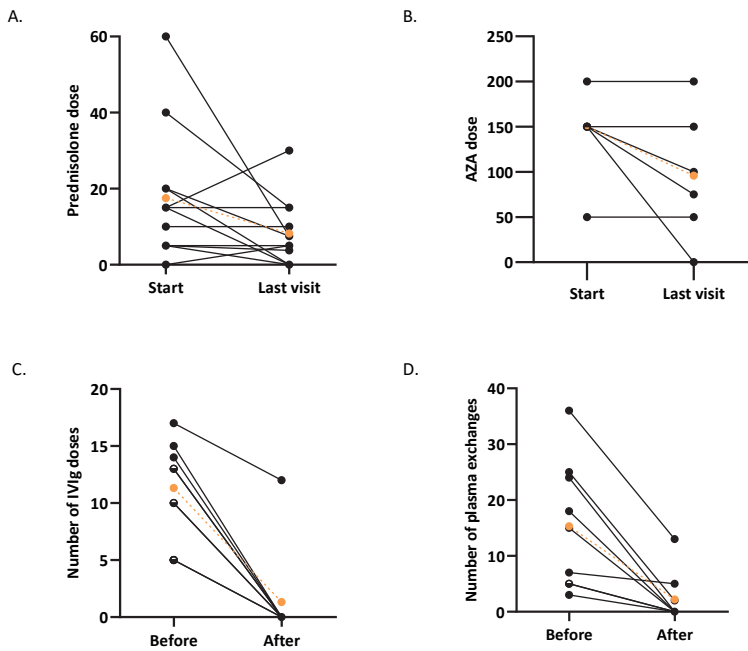
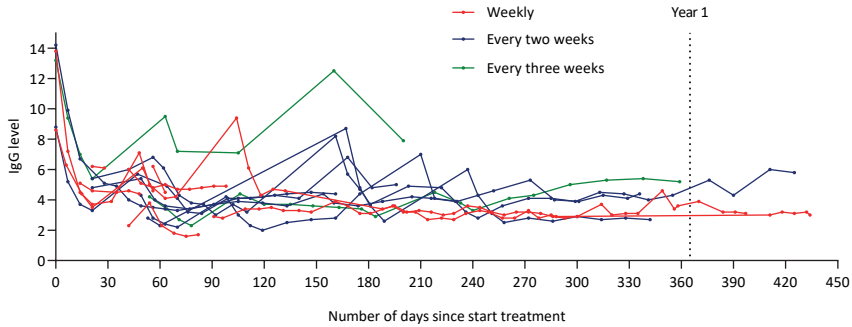


Figure 7.4 Change in prednisolone dose (panel A) and azathioprine dose (panel B) from start of efgartigimod to the last visit for each patient and change in number of IVIg doses (panel C) and plasma exchanges (panel D) in the period before and after start of efgartigimod for each patient
The orange line plot represents the mean change. Abbreviations: AZA, azathioprine; IVIg, intravenous immunoglobulin.

A.



B.

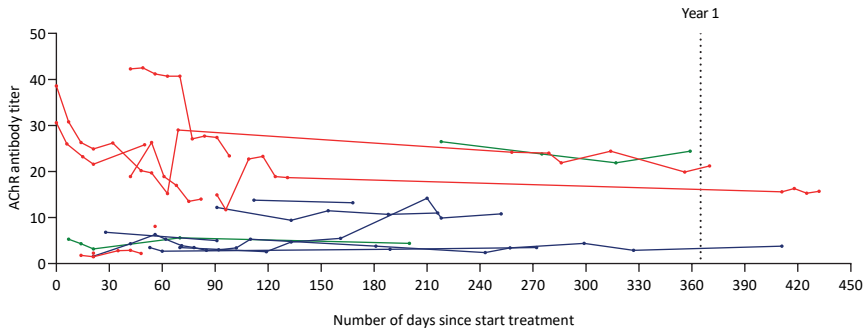


Figure 7.5 A. Serum immunoglobulin (IgG) levels and B. Acetylcholine receptor antibody titer after treatment with efgartigimod for each patient. Red, blue and green colors represent patients with different regimens of efgartigimod dosing at the last visit

IgG levels and AChR antibody titers determined within 4 weeks after treatment with IVIg and within 6 weeks after plasma exchange are excluded.

Discussion

In this retrospective study efgartigimod was effective for at least half of all patients; in 56% of patients a favorable outcome was seen at the last measurement, even though our cohort comprised only patients with refractory MG. The proportion of patients who were MG-ADL responders after 4 weeks of treatment was lower than in the ADAPT phase 3 trial (50% versus 68%).⁶² Even in a subgroup analysis of patients with refractory myasthenia gravis in ADAPT, the MG-ADL responder rate was higher (67.5%) than what was observed in our cohort.¹⁹² Other clinical outcome measures (a clinically meaningful improvement on MG-ADL, QMG, MGC and MG-QoL15r) were comparable to the results of the ADAPT-trial after 4 weeks.

The data in this cohort suggest that, in the long term, the effect of efgartigimod does not appear to persist; patients seem to exhibit a worsening of symptoms after 8-12 weeks of treatment (QMG, MGC and MG-ADL). This observation could suggest reduced effectiveness of efgartigimod, or it may be attributed to withdrawal of concomitant medication. In contrast, long-term results of the MG-QoL15r appear to indicate a persistent effect, and a significant number of patients (80%) were able to reduce other MG treatments such as prednisolone, azathioprine, plasma exchange and IVIg. However, a crucial caveat should be noted. The interpretation of these long-term effects is complicated by the diminishing number of patients contributing to the outcome over time, rendering these data less representative. Patients in our cohort required frequent dosing of efgartigimod. At the last visit, all patients switched to a one, two or three weekly frequency of administrations. Interestingly, with a regimen of more frequent administrations, IgG levels remained stable, and no further reductions below safety thresholds were seen.

This study has some limitations. First, we did not systematically evaluate side effects of efgartigimod in our dataset; however, no major adverse events occurred, and no patients discontinued efgartigimod due to side effects, indicating that efgartigimod was well tolerated. Secondly, several measurements had to be omitted from subsequent analyses because a substantial portion of patients (69%) underwent treatment with either plasma exchange or IVIg in the month before the initiation of efgartigimod. Consequently, the analyses of changes from baseline for both IgG levels and outcome measures are based on a limited number of patients and should be interpreted with caution. Thirdly, the determination of the AChR antibody titers was performed infrequently (**Figure 7.5**) and values were not always within the linear range of the assay. Therefore, it was not possible to correlate change in AChR antibody titers to the IgG levels or to clinical outcome measures. Lastly, due to the retrospective nature of this study, assessment of treatment outcomes was not mandatory and data from a considerable proportion of patients was lacking on various outcomes during the follow-up period, resulting in a potential risk of bias in the estimation of these outcome measures.

In conclusion, efgartigimod was shown to be effective in a relevant subset of patients with refractory MG. However, patients required more frequent dosing and fewer patients showed a significant improved MG-ADL response compared to the ADAPT trial. Our experience provides insights to better delineate the long-term effectiveness in a cohort of patients with refractory MG.

