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TITLE PAGE

TITLE: Efgartigimod efficacy and safety in refractory Myasthenia Gravis - UK's first real-world experience

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ABSTRACT

Background: We report our experience of patients with generalised MG (gMG) treated with Efgartigimod, an FcRN antagonist, under the Early Access to Medicine Scheme (EAMS) in the UK.

Methods: Data from all UK patients treated with Efgartigimod under the EAMS July 22-July 23 were collected retrospectively. Efgartigimod was administered as per the ADAPT protocol (consisting of a treatment cycle of 4 infusions at weekly intervals with further cycles given according to clinical need).

Results: 48 patients with AChR antibody-positive gMG were treated in 12 centres. Most (75%) were female and most had a disease duration of over 10 years. The average MG-ADL score at baseline was 11.2. Most (72.9%) patients had undergone thymectomy. 77.0% were taking prednisolone at baseline. All patients had utilized non-steroidal immunosuppressant treatments, the average number tried was 2.6 (range 1-6). 51% had received Rituximab. 54.2% of patients required regular IVIg/PLEX.

75% of patients had a mean reduction in the MG-ADL of ≥2 points in the first cycle and this remained stable throughout the study. The mean intracycle reduction in the MG-ADL score in the first, second, third and fourth cycles were -4.6, -3.9, -3.4 and -4.2 respectively. Side effects were generally mild. No rescue treatments were required. At the end of the study, 96% of patients remained on Efgartigimod.

Conclusion: Efgartigimod is a safe and effective treatment for patients with refractory, treatment-resistant gMG.

HIGHLIGHTS

- Efgartigimod is a human recombinant IgG1 antibody fragment that binds to the neonatal Fc receptor, thus inhibiting IgG recycling and reducing circulating IgG levels. The Phase 3 ADAPT trial compared Efgartigimod to standard of care and showed that Efgartigimod was a safe and effective in patients with generalised Myasthenia Gravis (gMG).
- Our study describes the UK real world of Efgartigimod in 48 patients with gMG who received treatment under the Early Access to Medicine Scheme, which showed, after one cycle of treatment, that 75% of refractory MG patients were defined as treatment responders. Efgartigimod was well tolerated, the proportion of patients with minimal symptom expression with successive treatment cycles and no rescue treatments were required during the study period.
- Efgartigimod is a safe and effective treatment for patients with refractory gMG, but further studies and ongoing real-world experience are required to determine which patients are most likely to respond to anti FcRN treatment and where exactly it should fit in the treatment pathway for gMG.

INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune disorder of the neuromuscular junction that causes fatigable neuromuscular weakness. Eighty-five per cent of patients have antibodies against the acetylcholine receptor (AChR) and a varying proportion of the remainder have antibodies against the post-synaptic clustering proteins – MuSK or LRP-4. A smaller proportion of patients are 'seronegative'[1].

The first line treatment for MG is pyridostigmine which can provide short-term symptomatic relief but has no disease-modifying effect[2]. Thymectomy is indicated in those who have a thymoma and to improve outcomes in those with younger onset seropositive generalized disease operatively will generally persist post-operatively[3]. Treatments such as Intravenous Immunoglobulin (IVIg) and Therapeutic Plasma Exchange (TPE) can improve symptoms rapidly, though the effects are short-lasting, and are generally reserved for acute severe exacerbations. The mainstay of management of MG rests on nonspecific broad-spectrum immunosuppression with steroids and non-steroid immunosuppressant therapies[2].

Despite these treatments, there is a clear unmet need for patients with MG[2]. Steroids, though effective, are associated with a plethora of well-documented side effects. Immunosuppressive agents have a slow onset of action and are not tolerated[4,5]. Approximately 15% of patients are refractory to standard therapies and may be dependent on costly treatments such as IVIg and TPE[6]. Real-world studies have shown that over 40% of patients with MG have unacceptable disease control[7] and MG is known to have a significant impact on quality of life[8].

A novel therapeutic target for MG that has emerged in recent years is the neonatal Fc receptor (FcRN). This is a ubiquitous MHC Class 1-like molecule that prolongs the half-life of IgG by allowing its recycling and thus protecting it from lysosomal degeneration. Efgartigimod (ARGX-113) is a human IgG Fab fragment that has been engineered to have a higher affinity for the Fc receptor than native IgG, thus reducing IgG recycling and lowering IgG levels in circulation. The mechanism of lowering IgG levels can be thought of as analogous to TPE which is widely used in MG but logistically difficult.

The efficacy and safety of Efgartigimod were demonstrated in phase 3 double-blind randomized placebo-controlled ADAPT trial[9]. Efgartigimod was given as an intravenous (IV) infusion weekly for four weeks with further cycles repeated as necessary, based on clinical progression. Efgartigimod was well tolerated and the primary outcome - a reduction of at least two points in the MG Activities of Daily Living (MG-ADL) scale sustained for more than 4 weeks in the first treatment cycle - was met.

Efgartigimod is now approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). It was licensed by the Medicines and Healthcare Products Regulatory Authority (MHRA) as an add-on therapy for patients with gMG in the United Kingdom (UK) in March 2023 but is not yet commercially available.

It has however been available under the Early Access to Medicines Scheme (EAMS) for adults with AChR-antibody-positive generalized MG who had failed, did not tolerate or were ineligible for standard treatments in specialist UK MG centres since May 2022.

The consensus achieved by UK-based MG specialists before the introduction of the scheme clinicians was that Efgartigimod would be reserved for patients with moderate to severe MG (MGFA Class IIIa to IVb), and its use was to be prioritised for patients with refractory disease (defined in this cohort as an MG-ADL ≥ 5 despite adequate treatment with ≥ 2 non-steroidal immunosuppressant agents, those who were intolerant or ineligible for such therapies or those patients who were dependent on IVIg and TPE). Efgartigimod was given as per the ADAPT trial treatment protocol as a 4-week cyclical treatment with retreatment timed according to patients' symptoms. The first cycle was always given in the hospital setting but a home care service was available in certain centres for subsequent infusions.

Our objective with this study was to provide the first real-world experience regarding the Efgartigimod efficacy, safety and tolerability in the UK population.

METHODS

Study design

This was an observational multicentre study designed to analyse the efficacy and safety of Efgartigimod in AChR antibody-positive generalised MG patients who were treated under the EAMS between July 2022 and July 2023 in the UK (which requires, according to the MGFA Task Force, that the Post-Intervention Status is unchanged or worse after corticosteroids and at least two other immunosuppressant agents, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by patient and physician).

Participants

All UK MG specialist centres were invited to provide anonymised data regarding patients treated with Efgartigimod between July 2022 and July 2023. The study was formally registered as an audit in each centre and Ethics approval was not required. All participants gave informed consent to participate in the study before taking part.

Outcomes

To allow comparison with the ADAPT trial, our primary outcome was the proportion of MG-ADL responders in the first cycle. Similar to the ADAPT trial, a patient was deemed a responder if there was at least a 2-point reduction in the MG-ADL score for 4 weeks[11]. We also sought to understand the variation of MG-ADL at different time points (day 0, day 22 and day 36) for each cycle, to describe the incidence of adverse events, to determine the need for rescue treatments and the rate of Efgartigimod discontinuation.

Health-related quality of life scales data was collected in some patients, but these data are presented descriptively as there were varying practices throughout the country with some centres using Myasthenia Gravis-Quality of Life 15 (MG-QOL 15) and others using MG-QOL 15r.

Statistical analysis

Statistical analysis was done using SPSS Statistics® version 28. Demographic data was presented descriptively, with mean values, standard deviation (SD), total number (N) and percentage (%). The variation of MG-ADL along the different time points, in each cycle, was analysed with a mixed linear model for repeated measures, assuming missing at random data. A p-value of <0.05 was considered statistically significant.

STROBE cohort checklist was used when writing our report[14].

RESULTS

Our analysis included 48 patients from 13 centres who had completed at least one cycle of Efgartigimod under the EAMS scheme in the UK by 20th July 2023. At the time, this represented 100% of MG patients who had completed at least one cycle of treatment. No patients were excluded from the analysis.

Most patients were female (75.0%, N = 36), with an average age of 49.2 (21.0 – 75.0, SD = 14.2) years old. The majority (66.7%, N = 32) had been diagnosed with MG more than 10 years before starting Efgartigimod. The average MG-ADL score at baseline was 11.2 (5 – 19, SD = 3.2). Most

patients (72.9%, N = 35) had undergone thymectomy in the past (mean time since thymectomy = 12.5 years, 1 – 38, SD = 8.3).

All patients had been treated with at least one non-steroidal immunosuppressant treatment (NSIST) in the past, and the average number tried prior to Efgartigimod was 2.6 (range 1 - 6). The most frequent NSISTs used included Azathioprine (79.2%, N = 38), Mycophenolate Mofetil (64.6%, N = 31) and Methotrexate (41.7%, N = 20). Six patients had received Cyclosporin, one had taken Tacrolimus and two had received Eculizumab. Just over half (52.1%, N = 25) had previously received Rituximab.

Seventy point eight per cent (N = 34) had previously received IVIg and 43.8% (N = 21) were still requiring it regularly at the time of Efgartigimod initiation. More than a quarter (27.0%, N = 13) had previously been treated within the previous year and 14.6% (N = 7) were still using it regularly at treatment initiation.

Just prior to the initiation of Efgartigimod, the majority of patients were taking a combination of NSIST and prednisolone (54.2%, N = 26). Ten patients were taking prednisolone only, and five were taking an NSIST only. Six patients were not on any immunosuppressive treatment at baseline though three of these patients were on regular IVIg. The NSISTs used included Azathioprine (7 patients), Mycophenolate Mofetil (14 patients), Methotrexate (8 patients) and Cyclosporin (2 patients). The average prednisolone dose was 20.5 mg daily (range 2-60 mg).

The reasons for starting Efgartigimod were listed as follows (participants could list more than one reason): persistent MG symptoms despite treatment (77.0%, N = 37), burden of treatment (35.4%, N = 17), dependence on IVIg/TPE (29.2%, N = 14), side-effects from previous treatments (12.5%, N = 6) and other reasons (4.2%, N = 2; participants specified needing bridging treatment). The detailed demographic and clinical data are available in Tables 1 and 2, respectively.

Table 1. Demographic and Clinical Data (N = 48)

Gender	
Female	36 (75.0%)
Male	12 (25.0%)
Age (years) (range, SD)	49.2 (21.0 – 75.0, SD 14.2)
Body mass index (range, SD)	32.3 (18.0 – 56.0, SD 9.2)
Time since diagnosis	
< 1 year	1 (2.1%)
1-5 years	11 (22.9%)
5-10 years	4 (8.3%)
More than 10 years	32 (66.7%)
Previous thymectomy Time since procedure (years) (range, SD)	35 (72.9%), 12.5 (1 – 38, SD 8.3)
Baseline MG-ADL score	11.2 (SD 3.2)
Number of previous NSIST used before current treatment (N patients)	48 (100%)
1	12 patients
2	13 patients
3	11 patients
4	7 patients
5	4 patients
6	1 patient

NSIST utilized prior to Efgartigimod (N patients)	
Azathioprine	38
Mycophenolate Mofetil	31
Methotrexate	20
Cyclosporin	6
Eculizumab	2
Tacrolimus	1
Rituximab	25 (52.1%)
Reason for starting Efgartigimod**	
Refractory MG	37 (77.1%)
Burden of treatment	17 (35.4%)
Dependent on IVIg/TPE	14 (29.2%)
Side-effects	6 (12.5%)
Other Reasons	2 (4.1%)
NA	2 (4.1%)

*Data presented in n (%), mean (SD) and median (IQR). Abbreviations: IQR – interquartile range; MG-ADL: Myasthenia Gravis Activities of Daily Living; NSIST: non-steroid immunosuppression. *The authors would like to add that some patients used one NSIST plus IVIg/TPE/RTX and were started on Efgartigimod afterwards. This follows the ADAPT trial, in which patients only had to be on a stable dose of at least one treatment for gMG (ie, acetylcholinesterase inhibitors, corticosteroids, or NSISTs) to be candidates for Efgartigimod. Furthermore, MHRA licensed Efgartigimod as an add-on to standard therapy for patients with AChR-positive. **More than one reason could be selected.*

Table 2. MG treatment at the time of commencing Efgartigimod and cycles completed (N = 48)

No immunosuppressive/immunomodulatory treatment	3
Prednisolone only	10
Prednisolone and NSIST	27
NSIST only	5
Regular IVIg with additional NSIST/prednisolone	18
Regular IVIg only	3
Regular PLEX	7
Steroid dose	20.5 mg/day (2-60 mg, SD 14.9)

Cycles

Cycles completed at data collection*	
First cycle	48 (100%)
Second cycle	32 (66.7%)
Third cycle	25 (52.1%)
Fourth cycle	14 (29.2%)
Reported side-effects	
First cycle	13 (27.0%), median severity grade = 1 (1-4)
Second cycle	8 (25.0%), median severity grade = 1
Third cycle	2 (8.3%), median severity grade = 1
Fourth cycle	0

Data presented in n (%), mean (SD) and median (IQR). Abbreviations: IVIg: intravenous immunoglobulin; IQR – interquartile range; MG-ADL: Myasthenia Gravis Activities of Daily Living; NSIST: non-steroid immunosuppression; TPE: plasmapheresis. *Patients started Efgartigimod in different time periods, which means that by the time data was collected, patients could be at different time points/cycles. Only one patient stopped Efgartigimod because of side effects.

In our cohort, 75.0% (36 patients, N = 48) were defined as MG-ADL responders in the first cycle. This percentage decreased slightly in the following cycles but then remained stable throughout the study: 65.6% were responders in the second cycle (21 patients, N = 32), 72.0% in the third cycle (18 patients, N = 25) and 64.3% in the last cycle (9 patients, N = 14). Four patients who were not responders on the first cycle responded to the second cycle.

The mean reduction in MG-ADL score at the end of each cycle (day 22) compared to the start (day 0) was, respectively, -4.6 points in the first cycle, -3.9 points in the second cycle, -3.4 points in the third cycle, and -4.2 in the fourth cycle (see Figure 1).

When ADL scores were compared to the ADL score prior to Efgartigimod initiation (day 0 of the first cycle), the mean reductions were: -4.6 points for cycle 1, -6.0 points for cycle 2, -6.9 points for cycle 3 and -7.8 points for cycle 4 (see Table 3).

Table 3. The mean difference in MG-ADL Scores comparing MG-ADL at baseline with the last day of each cycle

				95% Confidence Interval of the Difference	
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper
Cycle 1, Day 22 vs Baseline (N = 48)	-4.50000	4.11536	.59400	-5.69498	-5.30802
Cycle 2, Day 22 vs Baseline (N = 32)	-5.96875	3.64987	.64521	-7.28467	-4.65283
Cycle 3, Day 22 vs Baseline (N = 25)	-6.87500	3.68679	.75256	-8.43179	-5.31821
Cycle 4, Day 22 vs Baseline (N = 14)	-7.76923	3.53916	.98159	-9.90792	-5.63054

A two-way repeated measures ANOVA with a Greenhouse-Geisser correction was performed in the subgroup that completed three full cycles of Efgartigimod (N = 25). *Post-hoc* analysis with Bonferroni adjustment confirmed that there was a significant reduction in MG-ADL scores from baseline to the end of each treatment cycle. The complete analysis between each cycle is shown in Figure 2 and the full analysis of the MG-ADL score variation in the three cycles can be found in the supplementary material (Table 1).

Using an MG-ADL score of 0 or 1 to define Minimal Symptom Expression (MME)[12], we observed that 10.4% (5 patients, N = 48) of patients achieved this status by the end of the first cycle. The proportion increased with each cycle with 12.5% (4 patients, N = 32), 14.3% (4 patients, N = 25) and 35.7% (5 patients, N = 14) achieving MSE by the end of the second, third and fourth cycles respectively.

The timing of Efgartigimod treatment is bespoke with a varying time between the end of one cycle and the start of the next one depending on patient symptoms. The mean time interval between finishing the first cycle and starting the second cycle in our cohort was 6.4 weeks (3 – 15.7 weeks, SD 2.4). This interval decreased slightly between the second and third cycles [approximately 5.5 (3 - 10.9) weeks, SD 1.6] and between the third and fourth cycles [approximately 4.6 (3.0 – 6.7) weeks, SD 0.9]. MG-ADL variation within each cycle (calculated from the difference in MG-ADL at day 22 and day 0) was not correlated with interval duration.

Data regarding MG-QoL was only retrieved during the first cycle in 26 patients – we observed an average fall of 9.4 points (SD = 12.4) by day 21 (mean score of 22 points, SD = 15), starting from a mean score of 34 points (SD = 14).

More than a quarter (27.0%, N = 13) of the patients reported a side-effect on the first cycle, most of them were of mild severity. Three patients reported infections (SARS-CoV-2 infection and urinary tract

infection). Seven patients reported flu-like symptoms, one patient reported skin bruising and another reported reduced sensation in the lower legs.

No patients in this study required rescue treatment with IVIg or TPE. Two patients dropped out from this study – one of them did not show any improvement with Efgartigimod after one cycle, and the other patient had a severe adverse reaction (hypokalaemia), which was considered to be related to Efgartigimod administration. No deaths were reported.

DISCUSSION

This is a retrospective real-world study that captured all Efgartigimod-treated patients in the UK from May 2022 to July 2023. The cohort treated were those with long-term MG who had persistent symptoms despite standard treatment. The disease duration in the majority of patients was over 10 years, most patients had been on multiple immunosuppressant agents, more than half of patients had received Rituximab, and 54.2% (N = 26) required regular IVIg and/or TPE.

In this group of patients with severe MG, 75% of those treated with Efgartigimod were defined as MG-ADL responders with a clinically meaningful reduction in the MG-ADL score seen with each cycle. Though the numbers are small there seemed to be an accumulation of responses with average lower baseline scores at the start of the fourth cycle compared to that at the start of the first cycle.

No patients required rescue treatment with IVIg or TPE and no patients had an unplanned admission because of their MG. Efgartigimod had an IVIg and TPE-sparing effect in patients previously dependent on these treatments. In particular, it is interesting to review the patients who were previously dependent on TPE (N = 7) suggesting that anti-FcRN treatment was more efficacious or better tolerated in this cohort and further TPE cycles were not required.

In our population, Efgartigimod seemed to be relatively safe and well tolerated. Although about a quarter of patients reported mild side effects after the first cycle these were generally mild. One patient had a severe metabolic disturbance with hypokalaemia which was considered to be related to Efgartigimod, although the physiological explanation for this is unclear and no case reports or drug company notifications exist on this matter.

We observed an excellent response in a few patients (for instance, one patient whose baseline MG-ADL score was 11, falling to 0 at the end of the first cycle before increasing to 4 at the beginning of the second cycle but thereafter remaining ≤ 2. However, some patients did not have any demonstrable response (for instance, the one patient who dropped out of the study after the first cycle because no difference in the MG-ADL score was observed). We were not able to determine any factors that predicted a response to Efgartigimod.

Efgartigimod is a cyclical treatment with re-treatment timings dependent on symptom re-emergency.

The interval between treatments declined after the first cycle – likely because the patient and clinician could predict when the symptoms were likely to deteriorate and adjusted the timing of the next cycle to pre-empt the worsening of symptoms

There are some limitations to our study. Although it captured all patients treated with Efgartigimod in the UK between July 2022 and July 2023, the sample size is small and our average duration of follow-

up from the first cycle is 130.9 days (47 – 207, SD 43.2). It was a real-world study with a heterogeneous group of patients. Our study was not designed to analyse what factors were associated with response to Efgartigimod. There were no definite criteria for inclusion in the study other than AChR-antibody-positive generalized disease that was not adequately controlled on standard therapies and depending on access to clinical trials, clinical experience, and access to infusion centres facilities, individual sites may have had different thresholds for patient inclusion. Moreover, the timing of Efgartigimod treatment is variable and dependent on the clinicians' and patients' assessment of their disease severity.

These are early data and we do not have long-term follow-up data yet to quantify the steroid-sparing effect of Efgartigimod nor do we have data regarding the reduction of other immunosuppressive agents. Ongoing data collection will help to determine this. It is however the experience of many of the authors of this study that prednisolone dose can be reduced in patients who have demonstrated a response to Efgartigimod.

Our findings are broadly in keeping with those of the ADAPT study[9], though our patient cohort was slightly different, the average disease duration was longer in our cohort and our patient had a higher burden of previous treatment.

Our findings were also in keeping with real-world data from elsewhere including real-world studies from Italy (19 patients)[13] and Israel (22 patients)[14]. Small numbers of seronegative and MuSK patients were included in the Italian study. In the UK, Efgartigimod is only licensed for AChR-positive MG patients though the ADAPT trial did include MuSK-positive and seronegative patients. There is a rationale for the use of Efgartigimod in these groups, but they have not been studied in detail to date.

Our study does not answer the question of where Efgartigimod should fit in the treatment pathway. All our patients had ongoing severe symptoms as defined by MG-ADL scores and the MGFA status and the average disease duration was more than 10 years. Some guidelines would advocate for the earlier use of targeted therapies in severely affected patients[15]. Under the EAMS, Efgartigimod was available for patients with moderate to severe MG and therefore patients in crisis (MGFA Class V) were excluded. There have been no trials to demonstrate efficacy of Efgartigimod in Myasthenic Crisis but our data, which show the quick onset of action of this drug, suggest that this is a scenario where anti FcRN use could be explored in the future.

Under the early access to medicine scheme costs of the drug and home administration were funded by the pharma company. However, the costs of targeted therapies such as Efgartigimod must be borne in mind when considering their place in the treatment algorithm.

CONCLUSION

Efgartigimod was an efficacious and safe drug for patients with longstanding difficult to treat MG. However, questions remain including the characteristics of patients that are more likely to benefit from Efgartigimod or other FcRNs, its place in the treatment pathway and the concordant use of other immunosuppressant drugs. Larger prospective collaborative studies are also required to answer these questions of safety in real-world settings.

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CONTRIBUTORSHIP STATEMENT

Jennifer Spillane and Fiona Norwood conceived the study. All the authors contributed to data collection. Joana Dionísio and Jennifer Spillane performed the analysis and wrote the manuscript. Jennifer Spillane and Fiona Norwood supervised the project. All authors discussed the results and contributed to the final manuscript. Joana Dionísio is the guarantor for this paper.

ILLUSTRATIONS' LIST

ABBREVIATIONS

EMA: European Medicines Agency
FDA: Food and Drug Administration
IQR: interquartile range
IVIg: Intravenous Immunoglobulin
gMG: generalised MG
MG: Myasthenia Gravis
MG-ADL: Myasthenia Gravis Activities of Daily Living
NSIST: non-steroid immunosuppression treatment
SD: standard deviation
TPE: Therapeutic Plasma Exchange