Title

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Journal

Journal of managed care & specialty pharmacy, 30(6)

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Publication Date

2024-06-01

DOI

10.18553/jmcp.2024.30.6.517

Peer reviewed

Cost-effectiveness of eculizumab and efgartigimod for the treatment of anti–acetylcholine receptor antibody–positive generalized myasthenia gravis

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Plain language summary

Both eculizumab and efgartigimod provide more treatment benefits to patients with generalized myasthenia gravis compared with conventional immunosuppressive treatments, but at a higher cost. We used a mathematical model to estimate the long-term benefits and costs of these 2 new treatments relative to conventional therapy and assessed their alignment. To be considered cost-effective, eculizumab would need to be discounted by 93.01% and efgartigimod by 88.34% of the price that was used in the model's base case.

Implications for managed care pharmacy

This first cost-effective analysis comparing eculizumab and efgartigimod vs conventional therapy alone among patients with generalized myasthenia gravis in the United States showed higher quality-adjusted life-years and significantly higher total costs. The enormous incremental cost resulted from the high drug prices of these 2 newer treatments, whereas the impact of indirect benefit measured through productivity loss on the incremental cost was limited. Threshold price estimates could be considered to inform coverage decisions and optimize health care resource allocation.

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J Manag Care Spec Pharm.
2024;30(6):517-27

ABSTRACT

BACKGROUND: Eculizumab and efgartigimod were approved to treat anti–acetylcholine receptor antibody–positive generalized myasthenia gravis (anti–AChR Ab–positive gMG). These relatively new biological treatments provide a more rapid onset of action and improved efficacy compared with conventional immunosuppressive treatments, but at a higher cost.

OBJECTIVE: To assess the cost-effectiveness of eculizumab and, separately, efgartigimod, each added to conventional therapy vs conventional therapy alone, among patients with refractory anti–AChR Ab–positive gMG and those with anti–AChR Ab–positive gMG, respectively.

METHODS: A Markov model with 4 health states was developed, evaluating costs and utility with a 4-week cycle length and lifetime time horizon from a health care system perspective and a modified societal perspective including productivity losses from patients and caregiver burden. Model inputs were informed by key clinical trials and relevant publications identified from targeted literature reviews, and drug costs were identified from Micromedex Red Book. Costs and outcomes were discounted at 3% per year. Incremental cost-effectiveness ratios (ICERs; cost per quality-adjusted life-year [QALY] gained) were calculated for each comparison.

RESULTS: Among the corresponding populations, lifetime costs and QALYs, respectively, for eculizumab were $5,515,000 and 11.85, and for conventional therapy, $308,000 and 10.29, resulting in an ICER of $3,338,000/QALY gained. For efgartigimod, lifetime costs and QALYs, respectively, were $6,773,000 and 13.22, and for conventional therapy, $322,000 and 9.98, yielding an ICER of $1,987,000/QALY gained. After applying indirect costs in a modified societal perspective, the ICERs were reduced to $3,310,000/QALY gained for eculizumab and $1,959,000/QALY gained for efgartigimod.

CONCLUSIONS: Eculizumab and efgartigimod are rapidly acting and effective treatments for myasthenia gravis. However, at their current price, both therapies greatly exceeded common cost-effectiveness thresholds, likely limiting patient access to these therapies.

Myasthenia gravis (MG) is a chronic autoimmune and neuromuscular disease characterized by muscle weakness and fatigue that worsens after periods of activity. MG is a relatively rare disease, with an estimated prevalence of 14-20 per 100,000 people in the United States[1,2] and an annual incidence of 2.2 per 100,000.[3] With progression to generalized MG (gMG), patients experience fatigable weakness involving ocular, bulbar, limb, and respiratory muscles. The disease can be life-threatening and lead to worse functional status and higher health care resource utilization, such as hospitalizations, emergency department visits, intensive care unit visits, and feeding tube use.[4-9]

Based on serologic diagnosis, anti–acetylcholine receptor antibody–positive generalized myasthenia gravis (anti–AChR Ab–positive gMG) accounts for 85% of gMG. Generally, conventional treatment of gMG includes pyridostigmine, corticosteroids, and other immunosuppressive agents such as azathioprine and mycophenolate. However, patients may experience limited response or intolerance to these therapies, termed refractory gMG. Treatment for refractory gMG may include acute or chronic use of intravenous immunoglobulin or plasma exchange.[10,11] Rituximab may also be considered in patients with refractory gMG, although its efficacy is less certain in anti–AChR Ab–positive gMG.[10,11] New biological treatments regulating immune response serve as potential alternative therapies with a rapid onset of action and higher response rate, but at a higher cost.[12,13] Eculizumab is a monoclonal antibody against complement protein C5 that was approved by the US Food and Drug Administration (FDA) for the treatment of anti–AChR Ab–positive gMG in October 2017 with an annual cost of up to $450,000.[14] Efgartigimod is an immunoglobulin fragment that blocks the neonatal Fc receptor that was approved by the FDA in December 2021, also for the treatment of anti–AChR Ab–positive gMG, with a similar annual cost of up to $450,000 when dosed 13 cycles per year.[14]

In a review by the Institute for Clinical and Economic Review, published in September 2021, neither eculizumab nor efgartigimod was considered cost-effective compared with conventional therapies.[15] However, owing to the limited availability of data, these analyses were conducted using a placeholder price for efgartigimod. Additionally, the Institute for Clinical and Economic Review analysis included only the direct patient care costs as there was such limited information on indirect benefits of treatment for patients with MG. Given the potential impact of these therapies on caregiver burden or productivity losses, and to evaluate these treatments from a broader perspective, the current report addressed the indirect benefits of these new treatments by adapting estimates obtained from non-US sources. Also, given that the Institute for Clinical and Economic Review analysis was conducted prior to approval of efgartigimod by the FDA, the analysis evaluated all patients in the clinical trial, which included those with gMG, and anti–AChR Ab–positive gMG. However, the FDA approved efgartigimod only for those patients with anti–AChR Ab–positive gMG. Finally, the Institute for Clinical and Economic Review report included a shorter 2-year time horizon. This report improves on the point estimates of the Institute for Clinical and Economic Review report by updating all cost inputs, including the prices of eculizumab and efgartigimod, incorporating a societal perspective, updating clinical inputs for patients treated with efgartigimod to the FDA-approved population (ie, anti–AChR Ab–positive gMG), and extending the analysis to a lifetime time horizon.

The objectives of our analysis were to (1) evaluate the cost-effectiveness of eculizumab plus conventional therapy vs conventional therapy alone in the treatment of patients with anti–AchR-Ab–positive gMG, refractory to conventional therapy and (2) evaluate the cost-effectiveness of efgartigimod plus conventional therapy vs conventional therapy alone in patients with anti–AchR Ab–positive gMG, over a lifetime time horizon, separately evaluating a health care system and a modified societal perspective.

Methods

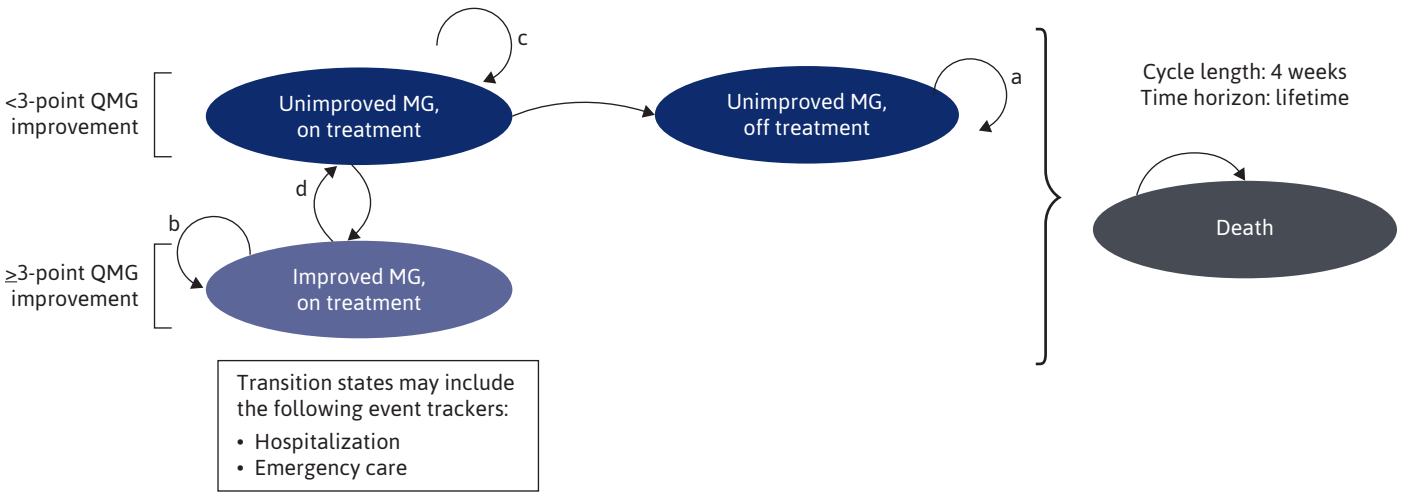
MODEL STRUCTURE

To evaluate our objectives, we modified a previously published Markov model (Figure 1) using 4-week cycles and a lifetime time horizon.[15] Costs and outcomes were discounted at 3% annually.

For eculizumab, the base-case evaluation involved patients with anti–AChR Ab–positive gMG in patients having failed 2 or more immunosuppressive therapies or at least 1 immunosuppressive therapy with either intravenous (IV) immunoglobulin or plasma exchange (PLEX) (refractory). For efgartigimod, the target population were all patients (refractory and nonrefractory) with anti–AChR Ab–positive gMG. Patients in either comparison received either eculizumab or efgartigimod plus conventional therapy, compared with conventional therapy alone. Conventional therapy consisted of cholinesterase inhibitors, corticosteroids, and/or other immunosuppressive treatments. Because of differences in patient characteristics in clinical trials and populations for which these treatments were approved, eculizumab was not directly compared with efgartigimod.

Patients entered the model at "Unimproved MG on initial treatment" Markov state (Figure 1). For the eculizumab base case, patients received eculizumab (900 mg IV on week 0, 1, 2, and 3; 1,200 mg at week 4; and 1,200 mg

FIGURE 1 Markov Model Structure



[a]*Patients who do not respond to initial treatment will transition to the unimproved MG off-treatment state and remain in this state throughout the future cycles.*
[b]*Patients who respond to initial treatment will transition to the improved MG on-treatment state and remain in this state throughout the future cycles, except for efgartigimod intermittent dosing in the scenario analysis.*
[c]*Only for eculizumab-treated patients: individuals with a less-than-3-point QMG improvement at 4 weeks remained in the "Unimproved MG on initial treatment" for 1 additional cycle, with a possibility of achieving treatment response by 8 weeks.*
[d]*In scenario analysis for efgartigimod intermittent dosing, patients would transition between unimproved and improved on initial treatment states.*
MG = myasthenia gravis; QMG = Quantitative Myasthenia Gravis score.

given every 2 weeks thereafter) plus conventional therapy, whereas the comparison population received conventional therapy alone. In the subsequent cycle, patients on eculizumab achieving a 3-point-or-better improvement in the Quantitative Myasthenia Gravis (QMG) score, considered a clinically meaningful improvement,[12,13,16] remained on treatment and transitioned to the "Improved MG on initial treatment" state. Patients with a less-than-3-point QMG improvement at 4 weeks remained in the "Unimproved MG on initial treatment" for 1 additional cycle, with a possibility of achieving treatment response by 8 weeks (as observed in the REGAIN trial[13]). At the end of 2 cycles, patients not achieving a 3-point QMG improvement discontinued the treatment and transitioned to the "Unimproved MG off-treatment" state. All living patients would remain in the "Improved MG on initial treatment" or the "Unimproved MG off-treatment" state for all future cycles.

For the eculizumab comparator, patients with response transitioned to the "Improved MG on initial treatment" after the first cycle, where they remained for all future cycles. Patients without response after the first cycle transitioned to an "Unimproved MG off-treatment" state. For the comparator, there were no additional transitions to the "Improved MG on initial treatment" after the first cycle.

For efgartigimod (10 mg/kg IV, dosed weekly) plus conventional therapy and its comparator (conventional therapy alone), patients transitioned to the "Improved MG on initial treatment" or the "Unimproved MG off-treatment" state based on treatment response after the first cycle only, consistent with what was observed in the ADAPT trial.[12]

Patients could transition to death from any living Markov state. There was no difference in mortality probability across all living states.

EVENT PROBABILITIES

Table 1 includes all event probabilities, costs, and utility inputs used in the model. The QMG was selected as the primary measure of treatment effect. It was preferred to the myasthenia gravis activities of daily living (MG-ADL), as it appears to have less of a floor effect and would therefore better characterize improvements in a patient with low baseline scores.[23] The probabilities of achieving a minimum 3-point improvement in QMG were derived from clinical trials by bootstrapping mean change in QMG at week 4 and week 8 for eculizumab (and its comparator) and week 4 for efgartigimod (and its comparator) using the mean and SD from clinical trials[12,13] and assuming a normal distribution for change in QMG. Changes in QMG score were bootstrapped for 1,000 individuals and the proportions of those with a 3-point-or-more QMG improvement

TABLE 1 Model Inputs

Model input			Input value	Range	Distribution
Transition probabilities					
Proportion of patients achieving 3-point-or-more reduction in QMG					
Treatment	Population	Timing			
Eculizumab	Refractory, AChR Ab+ gMG	Week 4	0.53[a]	0.35 to 0.79	Calculated
Eculizumab	Refractory, AChR Ab+ gMG	Week 8	0.58[a]	0.39 to 0.86	Calculated
CT (eculizumab comparator)	Refractory, AChR Ab+ gMG	Week 4	0.37[a]	Nonvarying	Nonvarying
Efgartigimod	AChR Ab+ gMG	Week 4	0.71[b]	0.46 to 1.11	Calculated
CT (efgartigimod comparator)	AChR Ab+ gMG	Week 4	0.26[b]	Nonvarying	Nonvarying
Efgartigimod	AChR Ab+ gMG	Week 8[c]	0.57[b]	Nonvarying	Nonvarying
Efgartigimod	gMG[c]	Week 4	0.73[b]	Nonvarying	Nonvarying
CT (efgartigimod comparator)	gMG[c]	Week 4	0.38[b]	Nonvarying	Nonvarying
Relative risk of patients achieving 3-point-or-more reduction in QMG					
Treatment	Population	Timing			
Eculizumab/CT	Refractory, AChR Ab+ gMG	Week 4	1.44[d]	0.96 to 2.15	Lognormal
Eculizumab/CT	Refractory, AChR Ab+ gMG	Week 8	1.59[d]	1.08 to 2.34	Lognormal
Efgartigimod/CT	AChR Ab+ gMG	Week 4	2.74[e]	1.76 to 4.27	Lognormal
Proportion of hospitalizations per cycle among those with unimproved MG			0.04[f]	0.01 to 0.07	β
Proportion of hospitalizations per cycle among those with improved MG			0.02[g]	0.01 to 0.04	β
Proportion of emergency department visits per cycle among those with unimproved MG			0.04[h]	0.01 to 0.08	β
Proportion of emergency department visits per cycle among those with improved MG			0.03[i]	0.01 to 0.04	β
QMG					
Baseline QMG			16.41[j]	15.48 to 17.34	Normal
Mean change in QMG from baseline among those with unimproved MG					
Treatment	Population	Timing			
Eculizumab	Refractory, AChR Ab+ gMG	Week 4	0.77[a]	−0.24 to 1.78	Normal
Eculizumab	Refractory, AChR Ab+ gMG	Week 8	0.51[a]	−0.52 to 1.53	Normal
CT (eculizumab comparator)	Refractory, AChR Ab+ gMG	Week 4	1.40[a]	0.42 to 2.39	Normal
Efgartigimod	AChR Ab+ gMG	Week 4	0.43[b]	−0.83 to 1.68	Normal
CT (efgartigimod comparator)	AChR Ab+ gMG	Week 4	0.38[b]	−0.25 to 1.01	Normal
Efgartigimod	gMG[c]	Week 4	0.31[b]	Nonvarying	Nonvarying
CT (efgartigimod comparator)	gMG[c]	Week 4	1.85[b]	Nonvarying	Nonvarying
Mean change in QMG from baseline among those with improved MG					
Treatment	Population	Timing			
Eculizumab	Refractory, AChR Ab+ gMG	Week 4	−6.95[a]	−7.98 to −5.92	Normal
Eculizumab	Refractory, AChR Ab+ gMG	Week 8	−7.25[a]	−8.27 to −6.22	Normal
CT (eculizumab comparator)	Refractory, AChR Ab+ gMG	Week 4	−6.53[a]	−7.62 to −5.43	Normal
Efgartigimod	AChR Ab+ gMG	Week 4	−8.90[b]	−10.07 to −7.74	Normal

continued on next page

TABLE 1 **Model Inputs** *(continued)*

Model input			Input value	Range	Distribution
CT (efgartigimod comparator)	AChR Ab+ gMG	Week 4	−4.93[b]	−5.68 to −4.18	Normal
Efgartigimod	gMG[c]	Week 4	−8.94[b]	Nonvarying	Nonvarying
CT (efgartigimod comparator)	gMG[c]	Week 4	−6.94[b]	Nonvarying	Nonvarying
Utilities					
Utility at baseline			0.47[k]	Calculated	Calculated
Increase in utility for each 1-point reduction in QMG score			0.03[l]	0.03 to 0.04	β
Intercept of the linear regression between QMG and EQ-5D			0.97[l]	0.92 to 1.03	β
Disutility of hospitalizations (applied for 1 week)			−0.22[m]	Nonvarying	Nonvarying
Disutility of emergency department visits (applied for 1 day)			−0.22[m]	Nonvarying	Nonvarying
Costs					
Eculizumab WAC Package Price in 2023			$6,523[14]	Nonvarying	Nonvarying
Eculizumab cost for first cycle (induction)			$50,879[n]	Nonvarying	Nonvarying
Eculizumab cost per cycle for subsequent cycles			$33,920[n]	Nonvarying	Nonvarying
Efgartigimod WAC Package Price in 2023			$6,069[14]	Nonvarying	Nonvarying
Efgartigimod cost per cycle			$34,596[n]	Nonvarying	Nonvarying
Eculizumab administration cost per IV injection			$65[17]	Nonvarying	Nonvarying
Efgartigimod administration cost per IV injection			$65[17]	Nonvarying	Nonvarying
Cost of vaccination for meningococcal infection			$98[o]	Nonvarying	Nonvarying
Cost per hospitalization			$32,551[p]	$31,533 to $33,586	γ
Cost per emergency department visit			$1,492[q]	$746 to $5,970	Imputed
Annual indirect cost saved from staying in improved MG			$10,000.00[r]	$0.00 to $60,000.00	Imputed

[a]*Bootstrapped value derived from the REGAIN trial.*[13]

[b]*Bootstrapped value derived from the ADAPT trial.*[12]

[c]*Data applied in scenario analysis.*

[d]*Calculated by dividing bootstrapped proportion of patients achieving 3-point-or-more reduction in QMG for eculizumab-treated patients by that of conventional therapy–treated patients, where the bootstrapped values were derived from the REGAIN trial.*[13]

[e]*Calculated by dividing bootstrapped proportion of patients achieving 3-point-or-more reduction in QMG for efgartigimod-treated patients by that of conventional therapy–treated patients, where the bootstrapped values were derived from the ADAPT trial.*[12]

[f]*Data obtained from the proportion of patients experiencing hospitalizations measured during 6 months prior to the time patients became refractory MG from the MGFA registry,*[4] *and further transformed into the proportion of the number of MG hospitalizations over a 4-week cycle.*

[g]*Data obtained from the proportion of patients experiencing hospitalizations measured during 6 months prior to enrollment to the MGFA registry*[4] *among nonrefractory patients, and further transformed into the proportion of the number of MG hospitalizations over a 4-week cycle.*

[h]*Data obtained from the proportion of patients experiencing emergency department visits measured during 6 months prior to the time patients became refractory MG from the MGFA registry,*[4] *and further transformed into the proportion of the number of emergency department visits over a 4-week cycle.*

[i]*Data obtained from the proportion of patients experiencing emergency department visits measured during 6 months prior to enrollment to the MGFA registry*[4] *among nonrefractory patients, and further transformed into the proportion of the number of emergency department visits over a 4-week cycle.*

[j]*Baseline QMG is the weighted average baseline QMG from the REGAIN*[13] *and ADAPT*[12,13] *trials weighted on the number of patients enrolled.*

[k]*Utility was calculated by fitting the baseline QMG in the linear regression model derived from Barnett's deidentified patient data to predict EQ-5D-5L on QMG.*[19]

[l]*Data derived from Barnett's deidentified patient data to predict EQ-5D-5L on QMG.*[18] *By inserting the baseline QMG (16.41) into the formula assuming linear association between EQ-5D and QMG (EQ-5D = 0.97446 − 0.03096*QMG), we obtained the EQ-5D at baseline as 0.47.*

[m]*Disutility was calculated by obtaining the difference in utility between admission and discharge from a study assessing acute illness and another study assessing chronic disease (heart failure), and the average of these 2 values was taken to be applied in both hospitalization and emergency department settings.*

[n]*Drug price was calculated with a 35% reduction for discounts and rebates.*[19]

[o]*Price was the average of 3 available vaccines (MENACTRA, MENVEO, and MENQUADFI) using the AWP Package Prices in 2023*[14] *with a 35% reduction for discounts and rebates,*[19] *applied only in patients receiving eculizumab.*

[p]*Data were obtained from the estimated cost per discharge for MG from a study in 2013 ($98,795)*[20] *and further inflated to dollars in year 2022.*[21]

[q]*Data were obtained from the estimated average cost per emergency department visit ($530) from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project in 2017*[22] *and further inflated to dollars in year 2022.*[21]

[r]*An optimistic value was imputed to generate an optimistic and potentially underestimated ICER.*

AChR Ab+ = acetylcholine receptor antibody positive; CT = conventional therapy; gMG = generalized myasthenia gravis; IV = intravenous; QMG = Quantitative Myasthenia Gravis score; WAC = wholesale acquisition cost.

calculated. Bootstrapped data were validated against one manufacturer's clinical trial confidential estimates provided to us for the proportions of those with a 3-point-or-more QMG improvement and utility data among efgartigimod-treated patients. The bootstrapped data were within 1.5% of the data from the clinical trial.

The probabilities of MG-related hospitalizations and MG-related emergency department visits among patients in different Markov states were obtained from a longitudinal cohort study assessing health care resource utilization among patients with refractory and nonrefractory gMG.[4] Data from refractory gMG were applied to the unimproved MG state; data from nonrefractory gMG were applied to the improved MG state. Age- and sex-specific mortality rates were collected from National Center for Health Statistics.[24]

UTILITIES

Utility values were derived from a deidentified data source consisting of 252 patients with complete QMG scores and EQ-5D-5L used in a previous analysis by Barnett et al.[18] The association between QMG and EQ-5D-5L was assessed using a univariate regression model. Markov state utilities were derived using estimated regression model parameters applied to the mean of the bootstrapped QMG changes for those with and without a minimum 3-point improvement in QMG (improved and unimproved MG, respectively). From the regression analysis, a baseline QMG score of 16.4 resulted in a utility of 0.47. Each 1-point improvement in QMG resulted in a 0.03 increase in utility. Therefore, a mean decrease in the QMG score of 8.90 points for efgartigimod at week 4 resulted in a utility gain of 0.27 to a utility of 0.74.

The disutility of MG-related hospitalizations and emergency department visits were obtained from a targeted systematic review of the literature. As no studies were identified in patients with MG, the disutility associated with hospitalizations for acute diseases[25] and heart failure[26] was used in this model. In the absence of a better estimate, this same disutility was applied to emergency department visits.

COSTS

Drug costs for eculizumab and efgartigimod were derived using wholesale acquisition cost,[14] with a 35% reduction for discounts and rebates.[19] Treatment administration costs were obtained using Current Procedural Terminology code 96365.[17] The cost of MG-related hospitalization was derived from literature estimates for MG-related health care costs for an MG-related inpatient claim in 2019.[20,27] The cost of MG-related emergency department visits was not available from any source. We therefore used the cost for a multiple sclerosis–related emergency visit, obtained from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project.[22] All costs were inflated to 2022 US dollars using the health care component of the Consumer Price Index.[21]

For the societal perspective, we conducted a systematic review of the literature to identify potential indirect benefits of treatment with eculizumab or efgartigimod. A single survey study was identified, conducted in Germany among adult patients with MG. Productivity loss from patients and their caregivers during the 12 months before and 4 months after study entry was assessed and valued at a daily wage using the human capital approach.[28] The calculated mean annual indirect benefit was $4,884 (€2,790 in 2009). To avoid potential underestimation, and to account for inflation and differences between salaries in Germany and the United States, we assumed a maximal societal benefit of $10,000 per person per year resulting from improved MG.

SENSITIVITY ANALYSIS

To characterize the uncertainty in our model, we performed 1-way, 2-way, and probabilistic sensitivity analyses on the base case. In 1-way sensitivity analyses, each model input was varied from the lower to the upper bound of its 95% CI.

Given the high uncertainty in indirect costs, we substituted the 95% CI with a minimum of $0 and maximum of $60,000 per year to evaluate a broader range of possible values.

The drug costs and indirect benefits of eculizumab and efgartigimod were varied simultaneously in a 2-way sensitivity analysis to evaluate the threshold drug prices required for each of these 2 treatments to be cost-effective compared with conventional therapy alone at incremental cost-effectiveness ratios (ICERs) of $50,000 to $400,000 per QALY gained.

We conducted a probabilistic sensitivity analysis using 1,000 iterations to evaluate the simultaneous impact of variability in all model inputs. Cost-effectiveness acceptability curves were used to display the proportion of simulation runs in which the drugs were found to be cost-effective compared with conventional therapy alone at varying levels of willingness-to-pay (WTP) thresholds.

SCENARIO ANALYSIS

Two scenario analyses were performed to assess the impact on cost-effectiveness of (1) changing the treatment population and (2) lengthening the dosing interval for efgartigimod. Specifically, to evaluate the potential change in cost-effectiveness due to off-label use of efgartigimod, we applied the full results from the broader gMG population included in the ADAPT trial.[12] In the second analysis, we assessed the impact of an intermittent dosing interval on

incremental cost-effectiveness. Using data from the ADAPT trial,[12] we assumed a once-weekly treatment schedule lasting 4 weeks and repeated every 8 weeks (4 weeks on, 4 weeks off). The model was modified to allow patients falling below the minimum 3-point QMG improvement during off-treatment periods to transition to an "unimproved MG" state, and transition back to an "improved MG" state when having QMG response during the next treatment cycle. Treatment response during the off-treatment period was derived from QMG reduction at week 8 from the ADAPT trial. Model inputs for scenario analyses are included in Table 1.

Results

BASE CASE

A summary of the base-case analysis results over a 10-year time horizon is presented in Table 2. All costs and ICERs were rounded to the nearest thousand. Among patients with refractory, anti–AChR Ab–positive gMG, when only direct costs were considered, the mean QMG for the lifetime time horizon was 12.70 for eculizumab vs 14.91 for conventional therapy alone. Treatment with eculizumab was more costly ($5,515,000 vs $308,000) and more effective (11.85 vs 10.29 QALY) compared with conventional therapy alone, resulting in an ICER of $3,338,000/QALY gained. When indirect costs were considered, the ICER was $3,310,000/QALY gained. To achieve an ICER of $200,000/QALY gained, the annual drug costs would need to be reduced to $31,500, or 6.99% of the base-case cost. Alternatively, at the base-case price, indirect costs would need to be $1,132,828 per year to achieve an ICER of $200,000/QALY gained.

Among patients with anti–AChR Ab–positive gMG, without considering indirect costs, the mean QMG throughout the lifetime time horizon was 10.21 for efgartigimod vs 15.41 for conventional therapy alone. Treatment with efgartigimod was also both more costly ($6,773,000 vs $322,000) and effective (13.22 vs 9.98 QALY) compared with the conventional therapy alone, yielding an ICER of $1,987,000/QALY gained. When indirect costs were considered, the

TABLE 2 Model Results for Base-Case and Scenario Analysis With a Lifetime Time Horizon

Analysis	Patient population	Cost components	Treatment	Drug cost	Total cost	Mean QMG	Mean number of MG-related hospitalizations	Mean number of MG-related ED visits	QALYs	Cost per QALY gained
Eculizumab										
Base case	Refractory AChR Ab+ gMG	Direct cost	ECU + CT	$5,217,000	$5,515,000	12.70	13.19	14.49	11.85	$3,338,000
			CT alone	$0	$308,000	14.91	14.59	15.90	10.29	
		Direct cost + indirect cost	ECU + CT	$5,217,000	$5,398,000	12.70	13.19	14.49	11.85	$3,310,000
			CT alone	$0	$234,000	14.91	14.59	15.90	10.29	
Efgartigimod										
Base case	AChR Ab+ gMG	Direct cost	EFG + CT	$6,464,000	$6,773,000	10.21	12.35	13.65	13.22	$1,987,000
			CT alone	$0	$322,000	14.06	15.29	16.59	9.98	
		Direct cost + indirect cost	EFG + CT	$6,464,000	$6,631,000	10.21	12.35	13.65	13.22	$1,959,000
			CT alone	$0	$270,000	15.41	15.29	16.59	9.98	
Scenario: Broader patient population	gMG	Direct cost	EFG + CT	$6,600,000	$6,908,000	10.01	12.25	13.55	13.35	$2,159,000
			CT alone	$0	$306,000	14.91	14.49	15.80	10.29	
		Direct cost + indirect cost	EFG + CT	$6,600,000	$6,762,000	10.01	12.25	13.55	13.35	$2,136,000
			CT alone	$0	$229,000	14.91	14.49	15.80	10.29	
Scenario: Intermittent dosing	AChR Ab+ gMG	Direct cost	EFG + CT	$3,243,000	$3,516,000	10.78	12.80	14.11	12.86	$1,108,000
			CT alone	$0	$322,000	14.06	15.29	16.59	9.98	
		Direct cost + indirect cost	EFG + CT	$3,243,000	$3,387,000	10.78	12.80	14.11	12.86	$1,082,000
			CT alone	$0	$270,000	14.06	15.29	16.59	9.98	

AChR Ab+ = acetylcholine receptor antibody positive; CT = conventional therapy; ECU = eculizumab; ED = emergency department; EFG = efgartigimod; gMG = generalized myasthenia gravis; QALY = quality-adjusted life-year; QMG = Quantitative Myasthenia Gravis score.

ICER was $1,959,000/QALY gained. To achieve an ICER of $200,000/QALY gained, the annual drug costs would need to be reduced to $52,578, or 11.66% of the base-case cost. Alternatively, at the base-case price, indirect costs would need to be $639,380 per year to achieve an ICER of $200,000/QALY gained.

SENSITIVITY ANALYSES

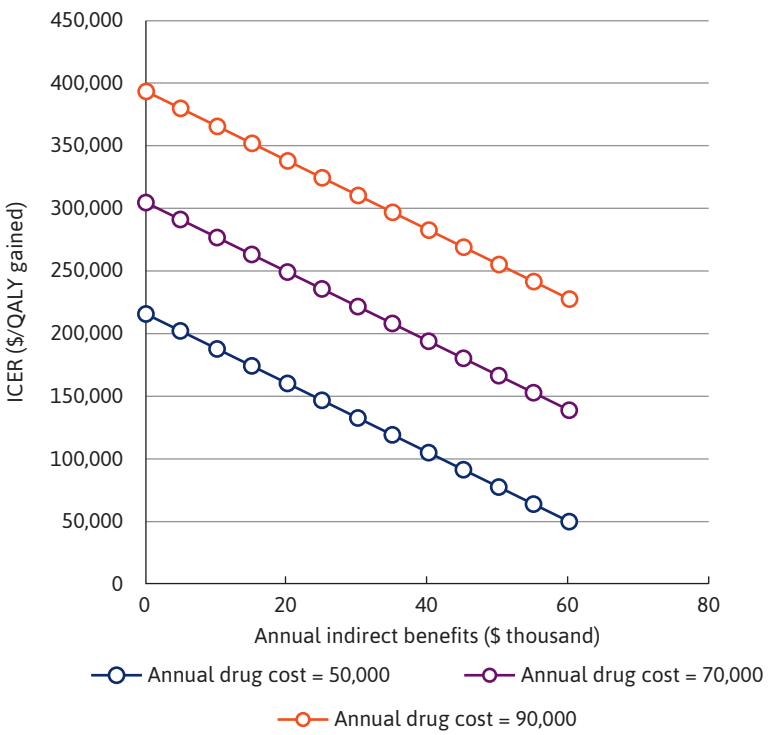
In 1-way sensitivity analysis, eculizumab results were most sensitive to the changes in (1) effectiveness of eculizumab achieving response relative to its comparator at week 8, (2) mean QMG change among comparator nonresponders at week 4, and (3) mean QMG change among eculizumab responders at week 8. For efgartigimod, the top 3 inputs affecting model results were (1) change in utility for each 1-point reduction in QMG score, (2) mean QMG change among efgartigimod responders at week 4, and (3) effectiveness of efgartigimod achieving response relative to its comparator at week 4. Among all 1-way sensitivity analyses, the minimum ICER achieved was $2,603,000/QALY gained for eculizumab and $1,674,000/QALY gained for efgartigimod (Supplementary Figures 1 and 2, available in online article).

In 2-way sensitivity analyses, across the different values of annual drug cost, higher annual indirect benefits resulted in lower ICER values (Figure 2 for efgartigimod and Supplementary Figure 3 for eculizumab). The probability of either eculizumab or efgartigimod being cost-effective compared with conventional therapy alone was 0.00%, at a WTP threshold of $200,000/QALY gained, regardless of considering the indirect costs (Supplementary Figure 4).

SCENARIO ANALYSIS

When the indication for efgartigimod was broadened to include all patients with gMG, lifetime total costs and QALYs were $6,908,000 (direct costs only), $6,762,000 (direct and indirect costs), and 13.35, respectively, compared with $306,000 (direct costs only), $229,000 (direct and indirect costs), and 10.29 for

FIGURE 2 Two-Way Sensitivity Analysis With Varying Indirect Cost and Willingness-to-Pay Threshold (ICER) for Efgartigimod Plus Conventional Therapy vs Conventional Therapy



To reach a willingness-to-pay threshold below the commonly accepted one, $200,000 per QALY gained, either the annual drug cost needs to be dropped to approximately $50,000 with indirect cost saved from staying at improved state for a full year to be $0, or the annual drug cost needs to be dropped to approximately $90,000 with indirect cost saved from staying at improved state for a full year to be $60,000.

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

conventional therapy. The resulting ICER was $2,159,000/QALY (direct costs only) and $2,136,000/QALY (indirect costs included) gained (Table 2).

Considering the effect of a longer efgartigimod dosing period (among patients with anti–AChR Ab–positive gMG), the lifetime total costs and QALYs were $3,516,000 (direct costs only), $3,387,000 (direct and indirect costs), and 12.86, compared with $322,000 (direct costs only), $270,000 (direct and indirect costs), and 9.98 QALY for conventional therapy. The resulting ICERs were $1,108,000/QALY (direct costs only) and $1,082,000/QALY (indirect costs included) gained (Table 2).

Discussion

Prior to the approval of eculizumab in 2017, there were no FDA-approved gMG therapies for more than 60 years. Given their unique mechanisms of action, eculizumab and efgartigimod both have a faster onset and higher response rate than available chronic therapies.[29] These therapies may be considered essential treatment options for those with insufficient response to or intolerance of conventional therapies. However, in our analyses, both treatments had ICERs that were far beyond the commonly acceptable WTP thresholds (up to $200,000 per QALY). To address uncertainties in our model, we conducted sensitivity analyses and scenario analyses, replaced key model inputs with the academic-in-confidence data provided by the manufacturer, and even applied a potentially overestimated $10,000 in annual indirect benefits from treatment among those with improved MG. Nonetheless, across all these approaches, the treatments remained well above cost-effectiveness thresholds.

Despite differences in model methods and assumptions, our findings that the price for eculizumab is not supported by treatment benefits are similar to a review of a manufacturer-submitted model evaluated by the Canadian Agency for Drugs and Technologies in Health (CADTH).[30] The model submitted to CADTH used a lifelong time horizon, lower discount rate (1.5% annually), and treatment response using MG-ADL measured at 6 months after treatment initiation. In this report, eculizumab had a cost-effectiveness ratio of Cad$1,329,219 per QALY for the sponsor's estimate and Cad$1,505,712 per QALY for CADTH's reanalysis, which primarily removed survival benefits resulting from improved gMG. Additionally, the model reviewed by CADTH assumed a treatment discontinuation rate due to nonadherence of 7.7% every 6 months, whereas treatment discontinuation due to noncompliance was not considered in our analysis.

Both eculizumab and efgartigimod were well beyond typical cost-effective thresholds, even after including substantial indirect costs in a modified societal perspective. In fact, data on indirect costs in the United States are lacking.[31] The best estimate that we could find was from a survey conducted in Germany, indicating an annual indirect cost of $4,884 (€2,790 in 2009) for those with gMG.[28] This estimate was calculated by multiplying the average daily salary (based on federal statistics) by the duration of productivity loss. Productivity loss included unemployment, underemployment, and caregiver productivity losses. Considering the average income in Germany is lower than that in the United States,[32,33] this calculated indirect cost may be slightly underestimated. Additionally, patients from this survey[28] had less severe gMG compared with those treated in the REGAIN[13] and ADAPT[12] clinical trials, resulting in a further potential underestimate of the indirect costs of gMG. Alternatively, our model assumed that these indirect costs were completely offset by treatment, an assumption that is optimistic and unlikely, resulting in a potential overestimate of indirect benefits.

This survey measured the indirect costs of gMG using the human capital approach. This approach uses the employee's perspective, capturing all lost work time and potentially overestimating the societal losses due to disease. An alternative approach, the friction method, takes the employer's perspective, tracking lost work time only until the initial production levels are re-established, such as when an employee is replaced. Although more difficult to calculate for this type of analysis, the friction method may be preferable when attempting to determine the societal impacts of illness. In our analysis, and considering all of these factors, we assigned an indirect benefit of $10,000 per year, a purposely optimistic estimate that is likely much higher than the benefit that would be realized from treatment with efgartigimod or eculizumab. We also conducted 2-way sensitivity analyses to ascertain the drug cost and indirect benefits needed for these therapies to achieve a cost-effectiveness threshold of $200,000 per QALY gained.

We also evaluated the cost-effectiveness of efgartigimod when the time between maintenance doses was doubled from every 4 weeks to every 8 weeks. Although the drug costs were halved, there was some loss of treatment effect, and QALYs gained with this approach, with approximately 14% of patients transitioning between the improved MG and unimproved MG states. Further, peak treatment effectiveness was used to estimate utility gains for patients in the "Improved MG" state, and declines in quality of life resulting from a longer dosing interval within that state were not captured in the model, resulting in a potential overestimation of treatment benefit. Similarly, patients transitioning to the unimproved state may have had their treatment effect underestimated. The ICER of this approach remained well

above typical cost-effectiveness thresholds, with efficiency gains being offset by decreased patient quality of life. More detailed data regarding the impact of extending the dosing interval are needed to improve the estimated cost-effectiveness of this therapeutic approach.

This study made several contributions to determining cost-effective treatment options for patients with anti–AChR Ab–positive gMG. First, to the best of our knowledge, this is the first cost-effective analysis for eculizumab conducted from a perspective of health care system in the United States and the first cost-effective analysis for efgartigimod performed since FDA approval was granted. Second, different approaches were modeled to best describe the experiences of eculizumab- and efgartigimod-treated patients. We also used the QMG instead of the MG-ADL to determine changes in patient health status. The QMG likely has less floor effects, resulting in a higher ability to detect changes in the measure at lower values.[23] Finally, we evaluated drugs costs required to achieve commonly accepted WTP thresholds, providing payers with better information for price negotiations.

LIMITATIONS

Our analysis had several important limitations to consider. First, the dosing schedule of efgartigimod was fixed. In the ADAPT trial,[12] dosing schedules after the first 4-weekly-infusion cycle were adjusted according to patient response, while a subsequent cycle could not be initiated earlier than 4 weeks after the end of the previous cycle. We partially addressed the impact of a variable dosing interval in a scenario analysis, although not allowing for individual variation in patient dosing depending on response. Second, our model inputs were primarily collected from clinical trials with relatively small sample sizes and greater uncertainty around estimates of treatment effectiveness. Owing to these small study sizes, there were limited or no data on the effectiveness of treatment in subpopulations. Finally, the long-term effects of treatment either were not available or were available from open-label trials without controls.

Conclusions

In the United States, either from a health care system or a societal perspective, neither eculizumab nor efgartigimod was considered cost-effective compared with conventional therapy alone. Access to these treatments in patients not receiving sufficient benefit or experiencing intolerable adverse events from conventional treatments may be limited by their prices.

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