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ORIGINAL RESEARCH

Post-Marketing Safety Concerns with Efgartigimod alfa: A Pharmacovigilance Analysis Based on the Food and Drug Administration Adverse Event Reporting System Database

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Aim: Efgartigimod alfa (EA) is a novel US Food and Drug Administration (FDA) approved neonatal Fc receptor-targeting drug; however, its real-world adverse event (AE) profile remains underexplored.

Methods: AE reports primarily related to EA were retrieved from the US FDA Adverse Event Reporting System database for the fourth quarter of 2021 to the third quarter of 2024. Disproportionality analysis using Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network, and Multi-item Gamma Poisson Shrinker algorithms was employed to detect signals of AEs.

Results: Our study processed 3,182 AE reports related to EA, revealing 57 signals that met the criteria of the ROR, PRR, Bayesian Confidence Propagation Neural Network, and Multi-item Gamma Poisson Shrinker algorithms across 14 system organ classes. Notably, the most significant signal in the System Organ Class was "Surgical and medical procedures", whereas the most significant signal in Preferred Term was "Bulbar Palsy". Some unexpected over-the-counter AEs, including falls, choking, sepsis, nephrolithiasis, and atrial fibrillation, were also observed. The median onset time of EA-related AEs was 101.5 d (interquartile range 27–260). The AE risk model associated with EA should be referred to as "early failure", with the likelihood of AEs decreasing over time.

Conclusion: This study highlights the potential AEs and risks associated with the clinical use of EA; the analysis provides significant evidence regarding the clinical safety of EA.

Keywords: efgartigimod alfa, myasthenia gravis, signal mining, adverse events

Introduction

Myasthenia gravis (MG) is an autoimmune disorder characterized by acquired neuromuscular junction transmission impairment mediated by autoimmune immunoglobulin G (IgG) antibodies.[1] MG seriously affects patients' work and life and reduces their quality of life. Patients with MG are currently treated with conventional immunosuppressive therapies, including glucocorticoids, such as methylprednisolone, and non-hormonal immunosuppressive agents, such as methotrexate and cyclophosphamide.[2] The symptoms of many patients can be effectively controlled with broad-spectrum non-specific immunosuppressive drugs such as glucocorticoids, cyclosporine, and tacrolimus.[3] For decades, acetylcholinesterase inhibitors and corticosteroids have been the cornerstones of treatment.[4] Moreover, intravenous immunoglobulin (IVIG) and therapeutic plasma exchange (PLEX) are capable of eliciting rapid therapeutic responses and alleviating symptoms in critical cases, and are frequently employed as first-line emergency treatments for MG crises.[5,6] Despite the critical role of immunosuppressive therapy in the management of MG, a significant proportion of patients, estimated at 10% to 20%, exhibit a lack of response to such therapy, thereby failing to attain complete or sustained remission.[7] In

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addition, the use of corticosteroids and other immunosuppressants is often accompanied by a range of potentially debilitating side effects,[8] such as osteoporosis and hypertension (HTN), alongside variable treatment efficacy.[9] Therefore, there is an urgent need to identify more effective drugs with fewer adverse effects for the treatment of MG.

In December 2021, efgartigimod alfa for intravenous use was first approved in the United States for the treatment of generalized MG (gMG) in adults with antibody-positive anti-acetylcholine receptors.[10] Efgartigimod is an Fc fragment of human IgG1 with enhanced affinity for the neonatal Fc receptor (FcRn) compared with endogenous IgG, resulting in reduced IgG recirculation and increased IgG degradation.[11] Efgartigimod significantly reduces IgG and acetylcholine receptor autoantibody levels in patients with MG.[12] This enables pathogenic IgG antibodies to be efficiently cleared from the body. Up to 88% of patients with MG progress to gMG within 2 years of disease onset.[13] A randomized, double-blind, placebo-controlled Phase 3 study demonstrated that efgartigimod rapidly improved health-related quality of life in patients with gMG.[14] A multicenter cohort study demonstrated that efgartigimod was an effective and well-tolerated treatment.[15] Additionally, a Real-World Evidence study has demonstrated that efgartigimod alfa is well-tolerated in clinical practice and can alleviate disability in patients with gMG.[16] Various studies have demonstrated the significant benefits of efgartigimod in the treatment of gMG. Efgartigimod alfa is a novel targeted biological agent that provides a new treatment option for adult patients with gMG.

Among the monoclonal antibodies targeting the immune system that have been approved for the treatment of gMG, notable examples include rituximab, eculizumab, and efgartigimod alfa. Rituximab is a humanized chimeric monoclonal antibody that targets the CD20 antigen.[17] Clinical studies have shown that rituximab can provide significant benefits for patients with refractory or severely gMG. However, it is important to note that rituximab has been associated with the risk of hepatitis C infection and reactivation of latent tuberculosis.[18] Therefore, comprehensive serological assessments are required prior to initiating treatment to mitigate these risks. Eculizumab is a monoclonal antibody that specifically targets the terminal complement protein C5, thereby inhibiting the release of pro-inflammatory mediators and the formation of the membrane attack complex (MAC). This mechanism effectively reduces complement-mediated damage to the neuromuscular junction. While clinical trials have demonstrated that eculizumab is both safe and effective for the treatment of refractory MG,[19] it is important to recognize that complement inhibition may also increase the risk of infections caused by encapsulated bacteria, such as Neisseria meningitidis.[20] In contrast to the aforementioned monoclonal antibodies, efgartigimod alfa exhibits a favorable tolerability profile, with headache being the most frequently reported adverse effect.[3]

Despite the promising applications of efgartigimod alfa in the treatment of autoimmune diseases, including gMG, its safety profile requires attention. The US Food and Drug Administration's Adverse Event Reporting System (FAERS), a database containing a wealth of post-marketing safety reports, provides an important resource for monitoring real-world adverse reactions to drugs.[21] This study used data mining techniques to analyze the adverse reaction signals of efgartigimod alfa in real-world applications, aiming to inform clinical drug use decisions.

Methods

Data Sources and Cleaning

In this study, the search terms "efgartigimod alfa", "efgartigimod alfa fcab", "Vyvgart", and "Vyvgart Hytrulo®" were used. The US FAERS database was searched for all reports listing efgartigimod alfa as a primary suspected (PS) drug from Q4 2021 through Q3 2024. Since efgartigimod alfa was approved by the Food and Drug Administration (FDA) for marketing in December 2021, all reports listing the drug as a PS drug during this period were included in our analyses, with no restrictions on sex, age, or nationality. The FAERS database comprises seven datasets: demographic and administrative information (DEMO), drug information (DRUG), adverse reaction events (REAC), therapy start and end dates (THER), indications (INDI), patient outcome (OUCT), and reported sources (RPSR). Data units from these sections were merged using R software. Because of the possibility of duplicate reports and irregularities in reporting during the submission process, downloaded raw data were cleaned to ensure reliability and quality. For example, when two reports shared the same CASEID (case ID), we retained the report with the most recent FDA_DT (report date). If two reports had the same CASEID and FDA_DT, we retained the report with the highest PRIMARYID (Report ID).[22] These data were used to analyze the association between efgartigimod alfa and potential AEs, as well as to assess their safety and associated risks.

Adverse Event Identification and Mining

Descriptions and classifications of AE reports were based on the Preferred Term (PT) and System Organ Class (SOC) as defined in the Medical Dictionary for Regulatory Activities terminology set (version 27.1), released by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.[23] Additionally, data on clinical characteristics, including sex, age, AE outcomes, country of report, and reporter occupation, were collected. In this study, AEs primarily associated with efgartigimod alfa were selected, and duplicate items were excluded to reduce bias in identifying AE risk signals. This study employed four methods for adverse drug event signal mining: the Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-Item Gamma Poisson Shrinker (MGPS) methods.[24–27] The ROR algorithm is widely used owing to its low bias and high sensitivity.[28] The PRR algorithm offers higher specificity than that of the ROR calculation method. BCPNN is a more advanced signal detection technique used globally; it is capable of early signal detection even with low or missing data, with results stabilizing as the number of reports increases.[29,30] However, this method is computationally complex and lacks transparency. The MGPS algorithm has the distinct advantage of detecting rare-event signals.[31] Our research synthesized these four algorithms, leveraging their unique strengths to multidimensionally enhance detection and confirmation. If at least one of the algorithms met the algorithm criteria, drug-related AEs were considered to have potential warning signs. When all four algorithms met the criteria, there was a more significant association between these AEs and the drug, helping to rule out non-true positive signals. The parameters for the four calculation methods were based on 2×2 contingency table calculations (Supplementary Table S1). The specific formulas and signal detection criteria are listed in Supplementary Table S2.

We used R software version 4.4.0 and Microsoft Excel 2021 for statistical analysis, with the "ggplot2" package in R software employed for plotting.

Time-to-Onset Analysis

We performed the Weibull proportionality test, a statistical method widely used for modeling event-time data, to analyze temporal changes in AE occurrence following efgartigimod alfa injection. This approach utilizes the Weibull shape parameter to test the hypothesis that AE incidence changes over time. The median time to AE onset and interquartile range were calculated to classify the type of drug-related AEs.[32]

AE occurrence time was calculated by subtracting the efgartigimod alfa start date (START_DT) from the AE start date (EVENT_DT). AE reports with incomplete, absent, or incorrectly formatted dates were excluded. Episode times were analyzed using the Weibull shape parameter test, with the proportion of events evaluated over time. The Weibull distribution is a continuous probability distribution characterized by a scale parameter (α) and a shape parameter (β). Onset-time analysis predicted the risk of AE occurrence over time based on these parameters. The predictions were classified into three categories: "early failure", "random failure", or "wear-out failure". If both the shape parameter and its 95% confidence interval (CI) are less than one, the risk of AE is estimated to decrease over time ("early failure"). If the shape parameter is approximately one and its 95% CI contains one, the risk of AE is considered constant over time ("random failure"). If both the shape parameter and its 95% CI are greater than one, the risk of AE is expected to increase progressively ("wear-out failure").[33]

Sex-Based Differences in Risk Signals for Efgartigimod Alfa

To analyze whether sex affects AEs associated with efgartigimod alfa, we used the ROR method to identify 15 PTs with a statistically significant incidence of AEs. These PTs, calculated after deleting missing values and meeting the criteria of the ROR algorithm, were categorized by SOC.

Drug Combination Analysis

We further analyzed the safety of efgartigimod alfa in combination with other conventional therapeutic drugs. The drugs used in combination were retrieved from all reports, including efgartigimod alfa (categorized as PS, Secondary Suspected, Interacting, and Concomitant drugs), and summarized according to customary clinical drug combinations

(acetylcholinesterase inhibitors, corticosteroids, or non-steroidal immunosuppressive therapies)[15] Initial results showed that triple therapy with efgartigimod alfa, prednisolone, and mestinon was the most common combination for treating gMG. Further disproportionality analyses were performed for this triple therapy. Higher values of log_2ROR and -log (p-value) indicated that combination therapy was more likely to cause specific AEs compared to efgartigimod alfa monotherapy. Additionally, to eliminate the potential confounding effects of concomitant medications on the outcomes of the combined treatment, we adjusted the model to account for the influence of prednisolone and mestinon. The adjusted results are presented in Supplementary Table S5.

Results

Basic Characteristics of Efgartigimod Alfa-Related Adverse Events

From Q4 2021 to Q3 2024, the FAERS database generated 5,122,390 AE reports, including 13,885,301 distinct adverse reactions and 17,720,498 drug-related PTs. After excluding 643,533 duplicate reports, 3,182 AEs were identified following the exclusion of reports listing Death and MG as PTs. A flowchart describing the AE screening process is shown in Figure 1.

A total of 371 cases (11.6%) were reported in male, 406 (12.8%) in female, and 2,405 (75.6%) with unknown sex. Age-specific data showed that 110 patients (3.5%) aged 18–65 years and 133 patients (4.2%) aged 65–85 years were

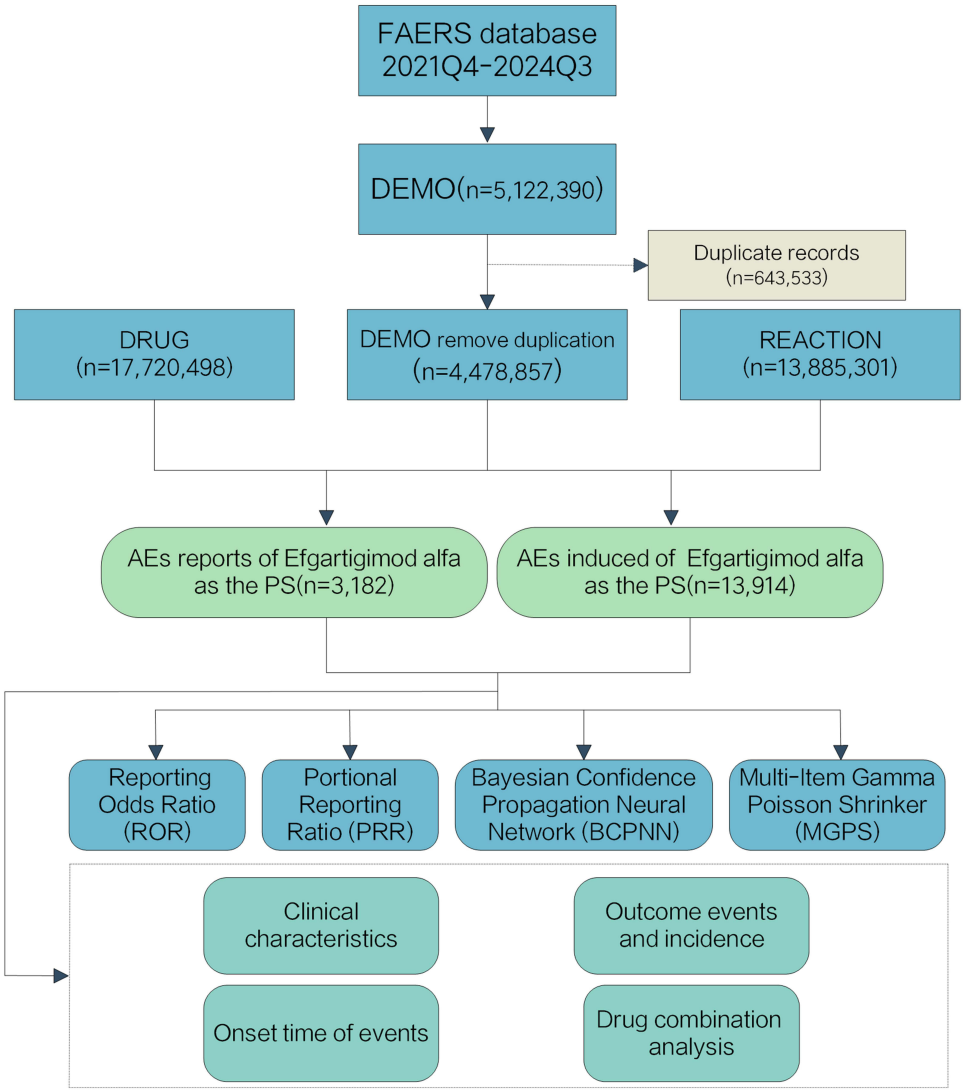

Figure 1 Flowchart for extracting and analyzing efgartigimod alfa-associated AEs from FAERS database.

Table 1 Clinical Character of Reports Associated with Efgartigimod-Alfa

Characteristics	Efgartigimod-alfa N (%)	Efgartigimod-alfa+ Prednisolone+ Mestinon N (%)
Number of reports	3182	152
Number of adverse events	13914	1296
Sex		
Female	406 (12.8)	12 (7.9)
Male	371 (11.6)	11 (7.2)
Missing	2405 (75.6)	129 (84.9)
Age(years)		
< 18	1 (0)	0(0)
18~65	110 (3.5)	5 (3.3)
65~85	133 (4.2)	10 (6.6)
>85	14 (0.4)	0 (0)
Missing	2924 (91.9)	138 (90.8)
Reporter		
Consumer	2475 (77.8)	112 (73.7)
Health professionals	297 (9.3)	31 (20.4)
Physician	303 (9.5)	7 (4.6)
Pharmacist	72 (2.3)	2 (1.3)
Missing	35 (1.1)	0 (0)
Reported countries		
United States	2692 (84.6)	142 (93.4)
Japan	204 (6.4)	0 (0)
Germany	52 (1.6)	0 (0)
Other countries	234 (7,4)	10 (6.7)
Serious outcome[a]		
Death	260 (8.2)	9 (5.9)
Disability	7 (0.2)	25 (16.4)
Hospitalization (initial or prolonged)	1274 (40.0)	64 (42.1)
Life-Threatening	145 (4.6)	14 (9.2)
Other Serious medical events	1079 (33.9)	40 (26.3)
Missing	417 (13.1)	0 (0)
Indications (top three)		
Myasthenia gravis	2203 (69.3)	135 (88.9)
Product used for unknown indication	554 (17.4)	17 (11.2)
Immune thrombocytopenia	21 (0.6)	0 (0)
Missing	380 (11.9)	0 (0)

Notes: [a] A report may have one or more outcomes of events.

reported, while age information was missing in 2,924 AE reports. The most common serious outcome was hospitalization (n = 1,274, 40.0%). A total of 92.1% of patients (n = 2,692) were reported in the United States, followed by 204 cases in Japan (6.4%). The most frequently reported indication for efgartigimod alfa was MG (n = 2,692). Demographic details and basic information on AEs associated with efgartigimod alfa are summarized in Table 1.

Signals of System Organ Classifications

Efgartigimod alfa-associated AEs were observed in 27 SOCs (Figure 2). Using the ROR, PRR, BCPNN, and MGPS algorithms, we identified two significant SOCs that met the criteria of all four algorithms: "Nervous System Disorders" and "Surgical and Medical Procedures". Detailed results are provided in Supplementary Table S3.

Signals of PTs

In our analysis, we excluded gMG-related comorbidities and detected 57 positive pharmacovigilance signals from 14 SOCs. A complete list of positive PT signals based on SOCs is available in Supplementary Table S4. We ranked these signals by the

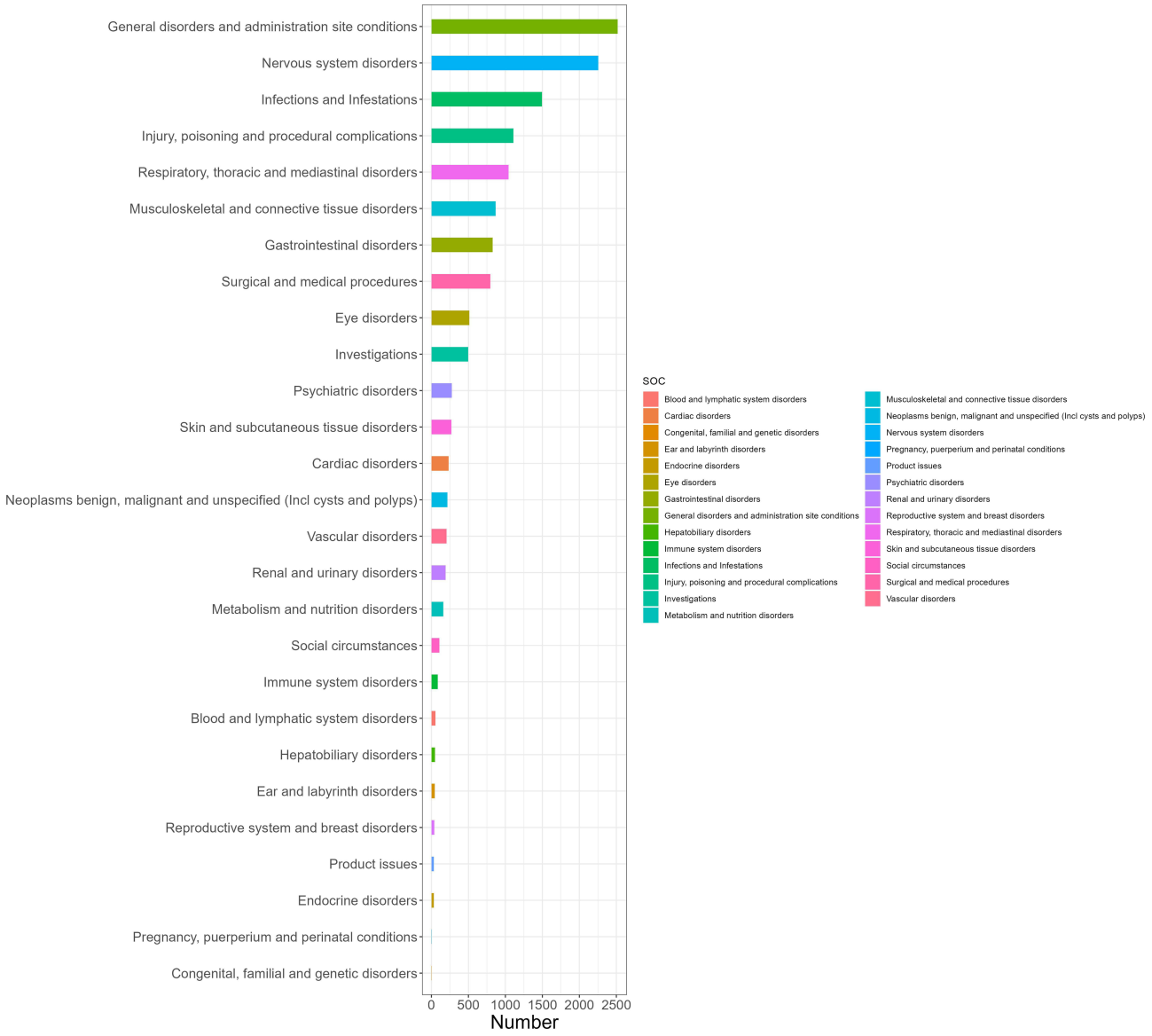

Figure 2 The number of efgartigimod alfa-induced AEs at the System Organ Class (SOC) level in FAERS database.

number of case reports. The top 24 AEs with the highest number of efgartigimod alfa-related reports are shown in Figure 3. Most of these positive signals were previously reported in clinical studies or listed in the drug's instructions. However, 16 positive signals—including Fall (n = 236), Sepsis (n = 64), Nephrolithiasis (n = 63), Atrial Fibrillation (n = 61), and Diverticulitis (n = 48)—were not mentioned in the drug's instruction manual or previous clinical trials.

Additionally, we ranked AEs by their IC_{025} values (Table 2 shows the top 20 PTs) and found that Bulbar Palsy (n = 12, IC_{025} = 6.85) and Herpes Zoster Reactivation (n = 4, IC_{025} = 3.5) had the strongest signals. Higher signal values indicate a higher likelihood of AE occurrence.

Results for Sex-Based Differences in Risk Signals

After excluding 2,405 AE reports with unknown sex, we analyzed 777 AE reports for sex-based differences. Results are shown in Figure 4. Our analysis revealed that "Symptom Recurrence" (ROR = 2.24 [1.08–4.66]), "Asthenia" (ROR = 1.21 [0.65–2.26]), and "Urinary Tract Infection" (ROR = 2.01 [1.02–3.96]) were more likely to occur in women after efgartigimod alfa use. By contrast, some high-risk AEs in men included: "Atrial Fibrillation" (ROR = 0.49 [0.18–1.35]) and "Dysarthria" (ROR = 0.35 [0.09–1.36]). These AEs were more frequent in men than in women.

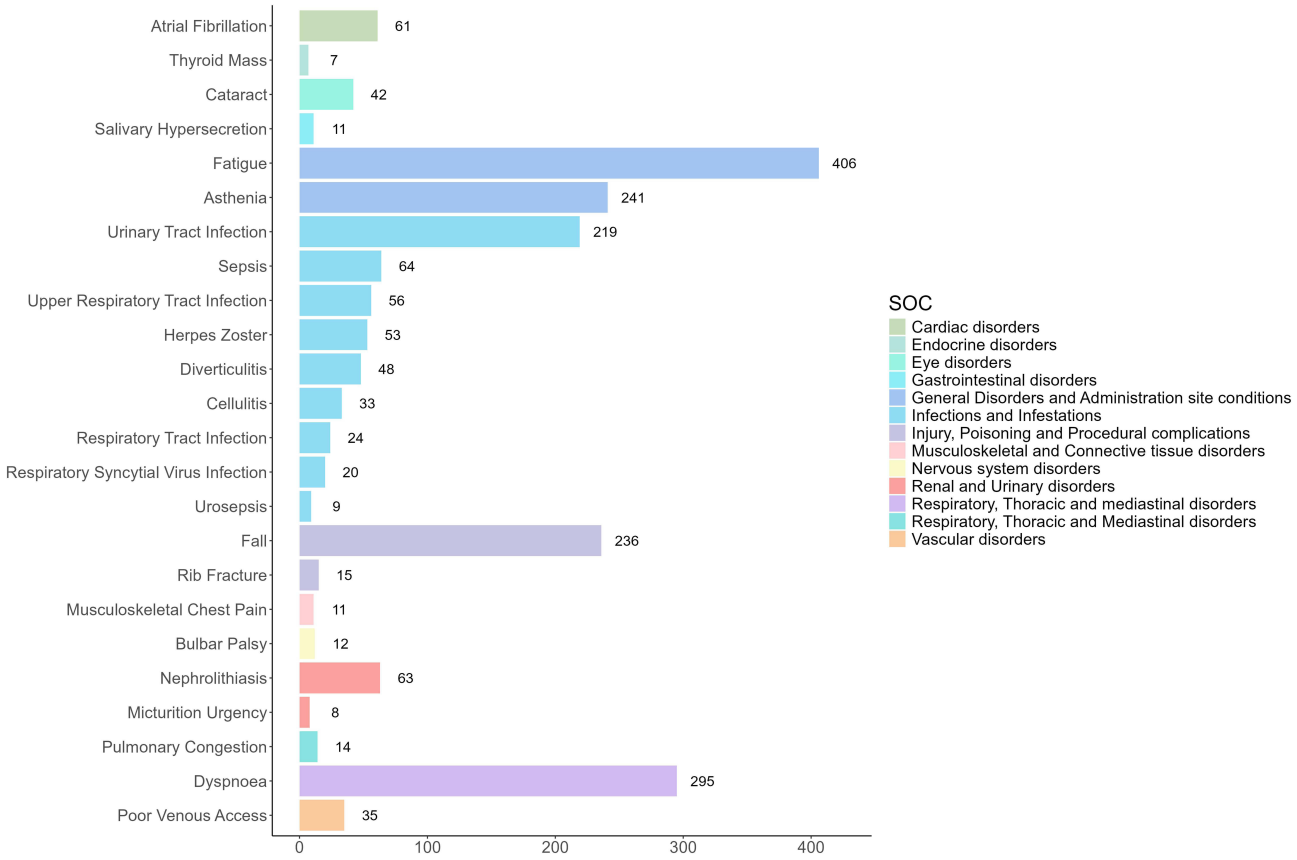

Figure 3 Bar plot shows the statistics of the signal PTs of reported adverse events.
Abbreviation: PT, Preferred Term.

Results for the Time-to-Onset Analysis

The temporal relation between drug administration and the onset of AEs is critical for assessing drug safety, as it identifies a specific window of risk and emphasizes the importance of preventing or diagnosing AEs early.[34] After excluding reports with incomplete dates, 844 reports were included in the time-to-onset analysis, with a median onset of 101.5 d (interquartile range: 27–260). The vast majority of AEs in these 844 reports occurred during the first 6 months of efgartigimod alfa treatment (Figure 5). Fitting the time-to-onset data to the Weibull distribution yielded a scale parameter of 153.33 (95% CI 140.15–166.51) and shape parameter of 0.83 (95% CI 0.78–0.87) (Table 3). These results indicate that the AE risk model associated with efgartigimod alfa aligns with an "early failure" pattern, meaning that the likelihood of AEs decreases over time. This finding

Table 2 Top 20 Preferred Terms Related to Efgartigimod Alfa Ordered by IC_{025} Value

PT	Case Reports	ROR (95%CI)	PRR(X^2)	EBGM($EBGM_{05}$)	IC(IC_{025})	Adjusted p
Bulbar palsy	12	272.1 (143.69–515.27)	271.86 (2544.48)	213.82 (125.32)	7.74 (6.85)	<0.001*
Herpes zoster reactivation	4	28.9 (10.69–78.11)	28.89 (104.68)	28.11 (12.23)	4.81 (3.5)	<0.001*
Temporomandibular pain and Dysfunction syndrome	3	30.21 (9.58–95.3)	30.21 (82.23)	29.35 (11.22)	4.88 (3.4)	<0.001*
Diaphragmatic disorder	3	24.52 (7.8–77.09)	24.51 (66.04)	23.95 (9.18)	4.58 (3.12)	<0.001*
Prostate infection	4	19.08 (7.09–51.33)	19.08 (67.24)	18.74 (8.19)	4.23 (2.92)	<0.001*
Epididymitis	4	18.3 (6.8–49.19)	18.29 (64.2)	17.98 (7.86)	4.17 (2.86)	<0.001*
Poor venous access	35	8.96 (6.42–12.5)	8.94 (244.58)	8.87 (6.71)	3.15 (2.66)	<0.001*
Diverticulitis	48	8.33 (6.26–11.07)	8.3 (305.75)	8.24 (6.49)	3.04 (2.63)	<0.001*
Colonic abscess	3	13.41 (4.29–41.91)	13.41 (34)	13.25 (5.11)	3.73 (2.27)	0.003

(*Continued*)

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Table 2 (Continued).

PT	Case Reports	ROR (95%CI)	PRR(X^2)	EBGM($EBGM_{05}$)	IC(IC_{025})	Adjusted p
Urinary tract infection	219	5.56 (4.87–6.36)	5.49 (802.58)	5.47 (4.89)	2.45 (2.25)	<0.001*
Catarrh	3	12.67 (4.06–39.59)	12.67 (31.85)	12.53 (4.83)	3.65 (2.19)	0.006
Nephrolithiasis	63	5.86 (4.57–7.51)	5.84 (251.22)	5.81 (4.72)	2.54 (2.18)	<0.001*
Upper respiratory tract infection	56	5.73 (4.4–7.45)	5.71 (216.4)	5.68 (4.56)	2.51 (2.12)	<0.001*
Amyotrophic lateral sclerosis	4	10.44 (3.9–27.97)	10.44 (33.78)	10.34 (4.53)	3.37 (2.07)	0.001
Respiratory syncytial virus infection	20	6.39 (4.12–9.92)	6.38 (90.25)	6.35 (4.39)	2.67 (2.03)	<0.001*
Eye contusion	5	8.16 (3.38–19.68)	8.16 (31.15)	8.1 (3.88)	3.02 (1.83)	0.001
Thyroid mass	7	6.91 (3.29–14.54)	6.91 (35.13)	6.87 (3.69)	2.78 (1.76)	<0.001*
Pulmonary congestion	14	5.37 (3.17–9.08)	5.36 (49.41)	5.34 (3.44)	2.42 (1.67)	<0.001*
Fall	236	3.59 (3.16–4.09)	3.55 (432.87)	3.54 (3.18)	1.82 (1.63)	<0.001*
Herpes zoster	53	4.09 (3.12–5.36)	4.08 (122.66)	4.06 (3.24)	2.02 (1.63)	<0.001*

Notes: *Adjusted p-value < 0.001 were considered statistically significant.
Abbreviations: ROR, reporting odds ratio; PRR, proportional reporting ratio; EBGM, empirical bayes geometric mean; CI, confidence interval; IC, information component; IC_{025}, the lower 95% CI, of IC; Adjusted p, Bonferroni-corrected p-values.

suggests that, during early treatment, increased vigilance is necessary to mitigate adverse effects, especially in patients with gMG.

Results for the Combination Analysis

From Q4 2021 to Q3 2024, the FAERS database recorded 152 reports of triple therapy with efgartigimod alfa, prednisolone, and mestinon. Using four algorithms, a disproportionality analysis was conducted to assess the safety profile of this combination therapy compared to efgartigimod alfa monotherapy for gMG. A total of 15 PTs met the algorithm criteria (Figure 6), with "Urinary Tract Infection" exhibiting the highest -log(p-value) and log_2ROR values. This suggests that urinary tract infection is more likely to occur in patients treated with combination therapy than in those receiving efgartigimod alfa monotherapy. Additionally, "Seasonal Allergy" was identified as a PT signal distinguishing triple therapy from monotherapy. We suggest that this association may be related to the indication for prednisolone.

Discussion

Intravenous efgartigimod alfa has been shown to significantly and rapidly reduce disease burden while improving muscle strength and quality of life in patients.[15,35,36] A recent meta-analysis demonstrated that anti-FcRn therapies are significantly more effective than complement inhibitor therapies, with efgartigimod emerging as the most favorable therapeutic option. However, that study did not analyze drug safety issues.[37] Among marketed drugs that promote the elimination of pathogenic antibodies by antagonizing FcRn, a systematic review and Bayesian network meta-analysis

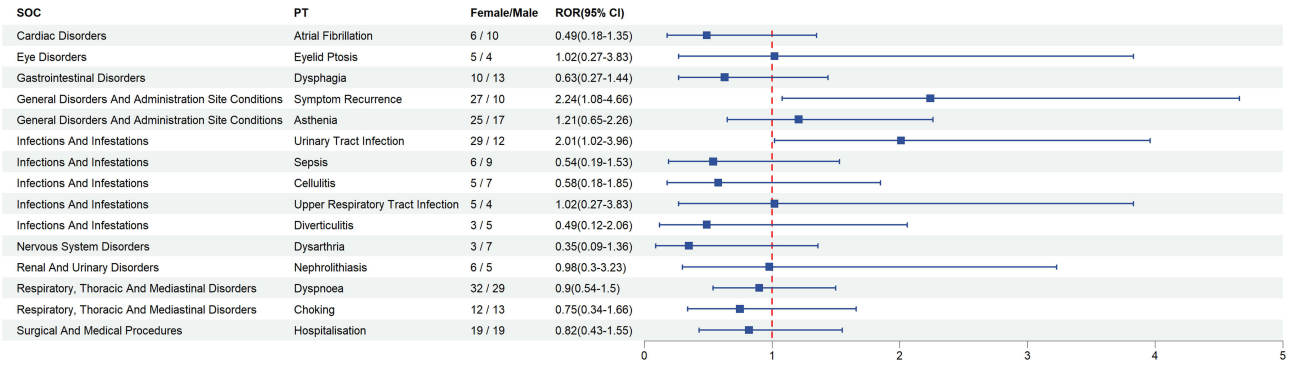

Figure 4 Forest plot of the signal AEs (based on the ROR calculation) risk signals for efgartigimod alfa.
Abbreviation: ROR, Reporting Odds Ratio.

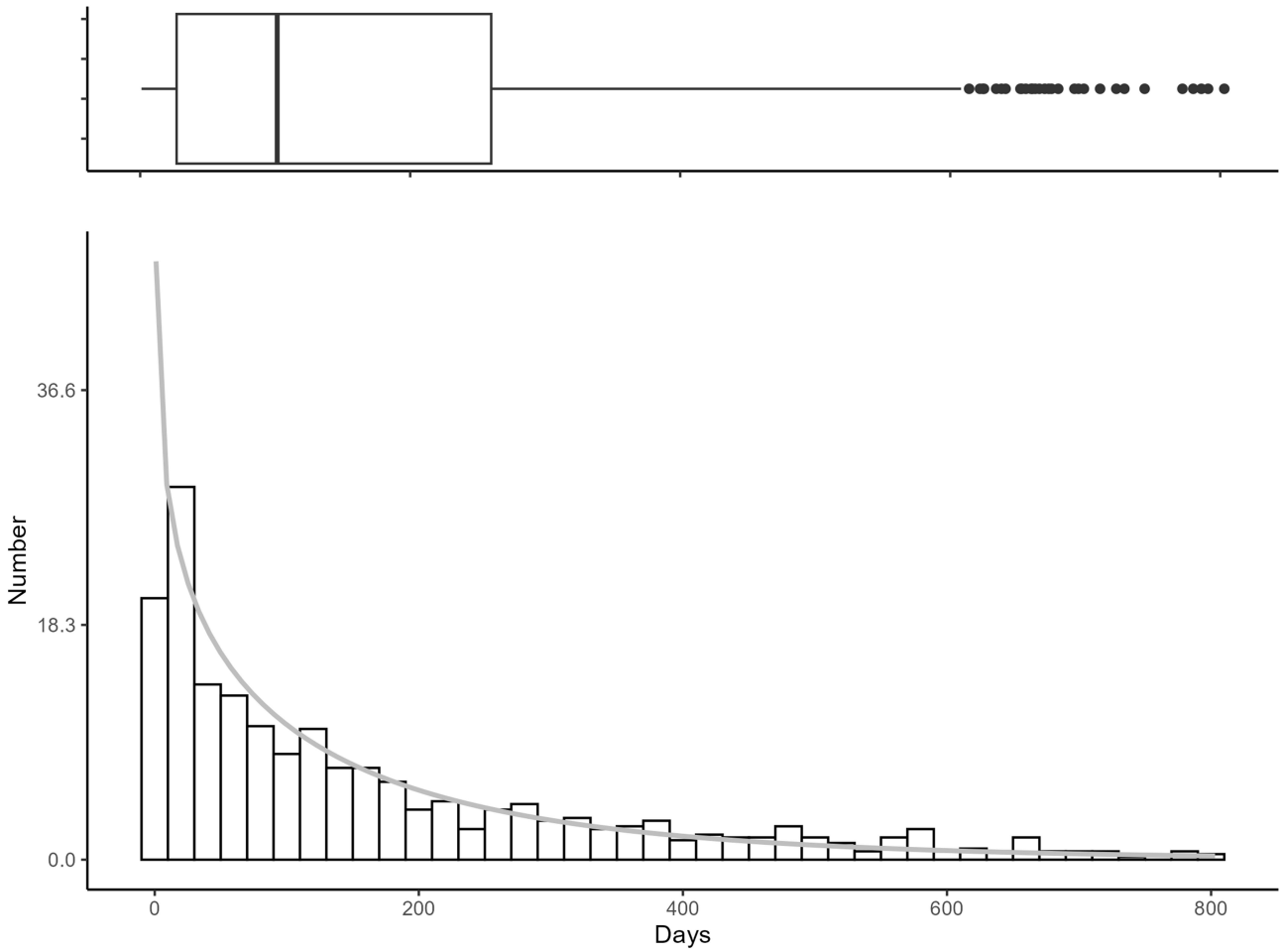

Figure 5 Histogram of time to onset of AEs to efgartigimod alfa.

identified efgartigimod alfa as having the best efficacy and safety profile in its class, with a higher SUCRA value.[38] Nonetheless, patients treated with efgartigimod alfa may experience unique adverse events requiring intensive monitoring to ensure optimal efficacy and safety.

This pharmacovigilance study is the most comprehensive and systematic real-world investigation into the safety of efgartigimod alfa based on FAERS data. A detailed disproportionality analysis was conducted using postmarketing data nearly 3 years after efgartigimod alfa's FDA approval. The FAERS database documented 3,182 AE reports involving efgartigimod alfa as a PS drug.

In the signal analysis based on SOC, our study identified "Surgical and Medical Procedures" (n=796, IC_{025}=1.74) as the sole SOC that concurrently met all four calculation methods and exhibited the highest signal value. Consequently, we have collated the PTs that align with all four calculation methods within this SOC (see Supplementary Table S6). Among these, "Thymectomy" (n=29, IC_{025}=8.87) emerged as the PT with the most pronounced signal value. PTs such as "Hospitalisation" and "Mechanical Ventilation", which are also categorized under "Surgical and Medical Procedures", mirror the standard clinical workflows associated with the management of MG.

Based on a PT signal hierarchy analysis, our findings revealed that among the top 10 reported AEs, Falls (n = 236), Sepsis (n = 219), Nephrolithiasis (n = 64), Atrial Fibrillation (n = 63), and Herpes Zoster (n = 61) were not mentioned in the latest FDA-provided insert. Interestingly, symptoms, such as Fatigue (n = 406), Dyspnea (n = 295), and Asthenia (n = 241), which may be considered concomitant symptoms of gMG, should also be carefully monitored during clinical use. Reports of Urinary Tract Infections (n = 219) and Upper Respiratory Tract Infections (n = 56) were consistent with prior clinical trials and drug instructions.[15] Efgartigimod alfa administration reduces circulating IgG levels, increasing its

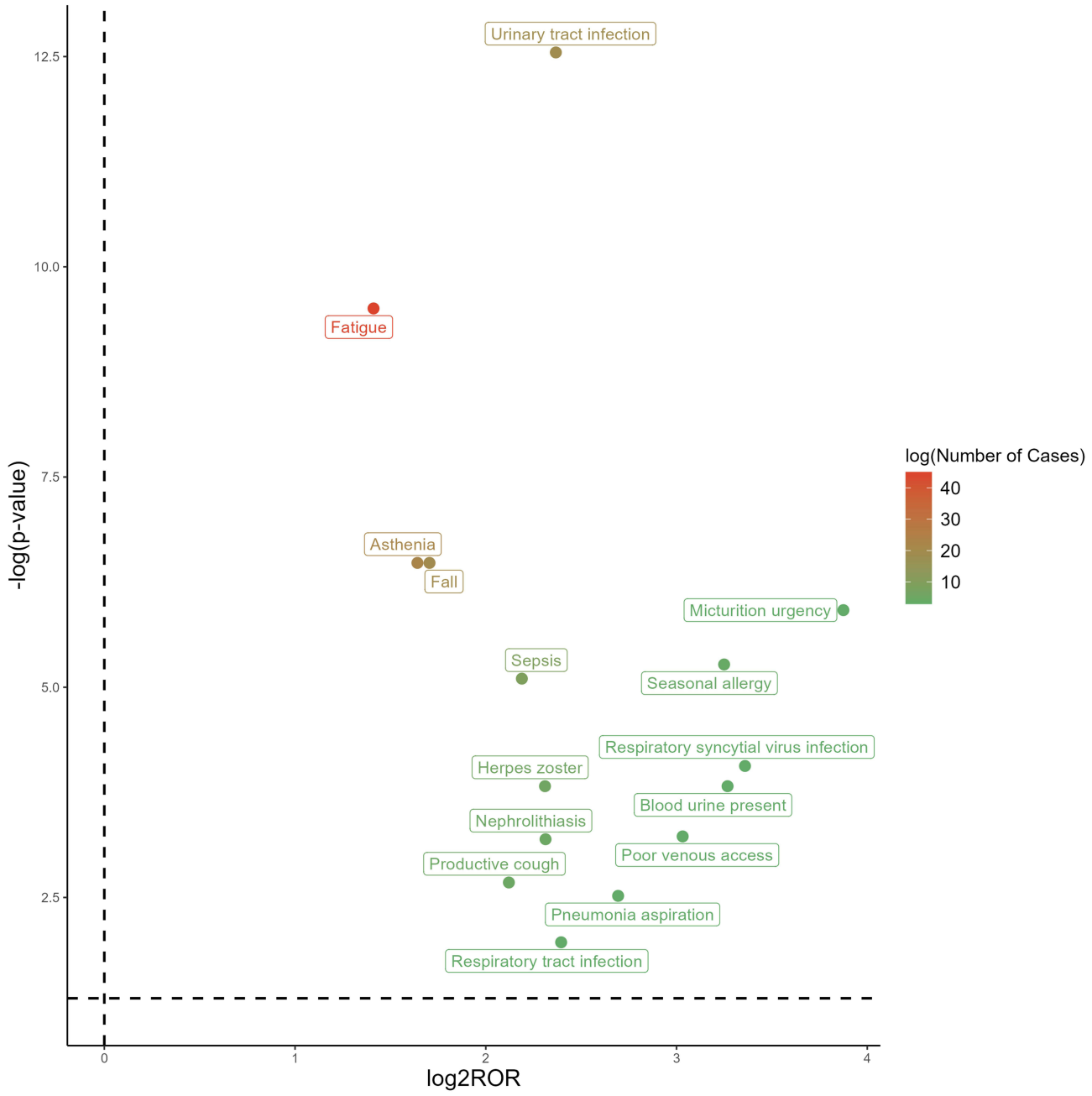

Figure 6 Volcano plots of the difference in PT signals for the combination analysis.

degradation without affecting albumin or other immunoglobulins. This reduction may impair the body's defense mechanisms, indirectly increasing the risk of infections, such as urinary tract infections.[39] Multiple experimental and real-world studies have shown that urinary tract infections are more likely to occur following efgartigimod alfa treatment.[15,40,41] Moreover, evidence suggests a potential link between urinary tract infections and the development of certain types of nephrolithiasis.[42,43] A recent multicenter, real-world cohort study in China reported a case of Herpes zoster in a patient treated with efgartigimod alfa.[11] Efgartigimod alfa functions as an FcRn blocker. Given that FcRn is implicated in IgG recycling and antigen presentation within antigen-presenting cells (APCs),[44] its blockade can augment IgG degradation and subsequently reduce IgG levels. This reduction might potentially exacerbate autoimmune conditions. Moreover, FcRn inhibition could diminish T-cell activation, thereby compromising the body's capacity to combat infections and predisposing patients to infection-related illnesses such as sepsis or Herpes zoster.

Table 3 Time-to-Onset Analysis for Signals with Efgartigimod Alfa

Drugname	Case Reports	TTO (Days)		Weibull Distribution				Failure Type
				Scale Parameter		Shape Parameter		
	n	Median(d) (IQR)	Min–max	α	95% CI	β	95% CI	
Efgartigimod alfa	844	101.5(27–260)	1–803	153.33	140.15–166.51	0.83	0.78–0.87	Early failure

Abbreviations: TTO, Time-to-onset; n, number of cases with available time-to-onset; IQR, interquartile range; CI, confidence interval; d, days; α, Scale parameter; β, Shape parameter.

We reordered the PT signals according to their IC_{025} value, as AEs with greater signal strengths warrant more attention during clinical medication. Herpes zoster reactivation (n = 4, IC_{025} = 3.5), prostate infection (n = 4, IC_{025} = 2.92), diverticulitis (n = 48, IC_{025} = 2.63), colonic abscess (n = 3, IC_{025} = 2.27), and respiratory syncytial virus infection (n = 20, IC_{025} = 2.03) are signals categorized as adverse reactions. Therefore, we suggest prioritizing the observation of infection-related issues when administering efgartigimod alfa.

The number of reports available for the sex subgroup analysis was limited because of missing information on the sex of most AE reports. The analysis of sex subgroups for efgartigimod alfa-associated AEs revealed slight differences between AEs occurring in women and men. These discrepancies suggest a potentially higher tendency for women to experience urinary tract infections following drug administration. Further research incorporating more comprehensive data is needed to clarify these findings in future studies.

The use of Weibull distribution analysis in pharmacovigilance provides a robust method for assessing the likelihood and timing of drug-related AEs.[45] Our study revealed that the time to AE onset for efgartigimod alfa follows an "early failure" model, indicating that AE incidence decreases shortly after the initiation of treatment, rather than being evenly distributed or increasing over time. Efgartigimod alfa-related AEs occurred predominantly within the first 3 months of treatment, with a median onset time of 101.5 d. Vigilant monitoring and proactive management of efgartigimod alfa-related AEs are therefore crucial, especially during the initial treatment phase. As the world's first approved FcRn antagonist, efgartigimod alfa offers several advantages, including shorter infusion times, long-lasting efficacy, and high clinical applicability. Additional indications (Primary immune thrombocytopenia and Chronic Inflammatory Demyelinating Polyneuropathy) for efgartigimod alfa are anticipated to gain approval in the future. Continued attention to emerging AE reports and ongoing epidemiological surveillance will remain essential.

Our study has several limitations. First, the FAERS database is subject to various biases, including reporting and indication biases, making it challenging to differentiate drug-induced AEs from the natural progression of the disease. Moreover, as a spontaneous reporting system, FAERS inherently encompasses several limitations that may introduce bias into disproportionality analyses. These limitations include missing data (such as the absence of sex and age information), incomplete information, arbitrary reporting, erroneous records, underreporting of AEs, geographical bias (with 84% of reports originating from the U.S), confounding by indication, and the potential for misinterpretation of causality. Second, the disproportionality analysis approach does not fully account for the confounding effects of comorbid medications and reveals only a statistical correlation—rather than a definitive causal relation—between the target drug and specific AEs. Therefore, further causal assessments are necessary. Thirdly, comorbidities can affect the response to MG treatment,[46] the lack of comorbidity data and the inability to determine the severity of the indication represent a major limitation of our study. This may introduce potential bias in interpreting the study results, as these factors can affect the assessment of confounding effects. Additionally, the one-year follow-up period is a limitation when it comes to assessing the long-term efficacy and safety of the study drug. Longer-term data are required to comprehensively evaluate the durability of the treatment effects and the potential for late-onset adverse events. Despite these limitations, the FAERS database offers the advantage of providing a broad, real-world dataset, enabling early detection of drug safety signals and trends across diverse populations. Its analysis remains clinically valuable for identifying potential drug risks.

Conclusion

Based on data from the FAERS database, our study found that efgartigimod alfa demonstrates a favorable safety profile, with most AEs being mild to moderate. We also explored the potential for preventing efgartigimod alfa-related AEs, particularly infection-related AEs, through vigilant therapeutic drug monitoring. Our study provides significant evidence regarding the clinical safety of efgartigimod alfa, and we hope that it will contribute to enhancing the safety of patients during their course of treatment.

Data Sharing Statement

Publicly available datasets were analyzed in this study. This data can be found here: https://fis.fda.gov/extensions/FPD-QDEFAERS/FPD-QDEFAERS.html.

Ethics Approval Statement

Since the FAERS database is accessible to the public and patient records are anonymized and de-identified, ethical clearance and informed consent are not required for this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to disclose for this work.

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