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# Therapeutic Ineffectiveness of Calcitonin Gene-Related Peptide Antagonists: A Real-World Pharmacovigilance Analysis

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## Abstract

**BACKGROUND/AIMS:** Migraine is treated with a variety of drugs with different pharmacological mechanisms of action. Among these drugs, calcitonin gene-related peptide (CGRP) antagonists represent a novel approach to the treatment of migraine. Aim of this study was to evaluate "drug ineffective" reports of CGRP antagonists obtained from an adverse event reporting system by disproportionality analysis.

**MATERIALS AND METHODS:** To ascertain the signal strength of the "drug ineffective" event associated with CGRP antagonists, reports available in Food and Drug Administration Adverse Event Reporting System (FAERS) until 31 December 2024 were included in the study. The OpenVigil 2.1-MedDRA-v24 software package was utilised for data mining and the analysis of disproportionality of these reports.

**RESULTS:** After data mining of reports in FAERS, it was found that there were 3,610 reports of small molecule CGRP receptor antagonists and 4,956 reports of monoclonal antibodies against CGRP related to drug ineffectiveness. Disproportionality analysis revealed that rimegepant [reporting odds ratio (ROR) 10.879; proportional reporting ratio (PRR) 6,708], ubrogepant (ROR 5,865, PRR 4,487), eptinezumab (ROR 5.7, PRR 4,397), and zavegepant (ROR 3,559; PRR 3,064) exhibited a positive signalling strength for drug ineffectiveness.

**CONCLUSION:** A retrospective review of reports of CGRP antagonist drugs that provide effective treatment for migraine showed that half of these drugs had a positive signal indicating drug ineffectiveness. However, this information, obtained using the pharmacovigilance database, needs to be supported by other studies conducted in the clinic.

**Keywords:** CGRP antagonist, drug ineffective, adverse event reporting system

## INTRODUCTION

Calcitonin gene-related peptide (CGRP) has been identified as an important mediator of vasodilation and pain in migraine patients. The administration of CGRP antagonists has been demonstrated to result in the termination of migraine attacks and the prevention of migraine occurrence.[1] There are currently two groups of drugs that act on CGRP in the treatment of migraine: small molecule CGRP receptor antagonists and monoclonal antibodies against CGRP.[2] All monoclonal antibodies against CGRP, including erenumab, fremanezumab, galcanezumab, and eptinezumab, as well as the small molecule CGRP receptor antagonist atogepant, are used in the prophylaxis of episodic and chronic migraine. Other small molecule CGRP receptor antagonists, rimegepant, are indicated for the prophylaxis of episodic migraine and the acute treatment of migraine. Ubrogepant and zavegepant are indicated only for the acute treatment of migraine.[3] The American Headache Society position statement lists CGRP-targeted migraine therapies as a first-line option for migraine prevention.[4]

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In recent years, there have been groundbreaking developments in migraine treatment.[5] Along with these advances in treatment, reports of therapeutic ineffectiveness have also been shown to increase over the years.[6] Furthermore, therapeutic ineffectiveness has been reported to be one of the main reasons for discontinuation of used migraine drugs.[7] Nevertheless, there are various drug groups with different mechanisms of action in the treatment of migraine, ineffectiveness varies even within these groups. For instance, clinical evidence demonstrates the efficacy of metoprolol and propranolol in the treatment of migraine, while acebutolol, which utilizes a similar mechanism, has been shown to be ineffective.[8] A network meta-analysis showed that monoclonal antibodies against CGRP were most effective and had fewer adverse effects compared to placebo, followed by small molecule CGRP receptor antagonists.[9] Nevertheless, ineffectiveness or serious adverse effects have been shown to affect the discontinuation of CGRP treatment.[10]

Adverse events (AEs), including 'drug ineffective' are defined as medically undesirable events resulting from the use of a pharmaceutical product. The most comprehensive database of AEs is the United States Food and Drug Administration's Adverse Event Reporting System (FAERS).[11] FAERS is a publicly accessible database containing real-world data on AEs. This database contains basic information on patients' demographic details, drug usage details, reporting sources, drug indications, and patient outcomes. The data are primarily submitted voluntarily by healthcare professionals and patients.[12] There are differences between patient and healthcare professional reports. Some studies have shown that patient reports may be similar to, or contain more detail than, healthcare professionals' reports.[13] It is important that changes in the effect of drugs are recorded in FAERS. Disproportionality analysis of the data obtained from large databases of spontaneous AE reporting systems such as FAERS has been an important method for drug safety monitoring.[14,15] Regarding pharmacovigilance, the proportional reporting ratio (PRR)[16] and the reporting odds ratio (ROR)[17] are the most popular methodologies utilized for the detection of AE signals. FAERS contains duplicate or incomplete reports. OpenVigil 2.1 is a software tool specifically designed for the extraction, cleaning, mining, and analysis of AE data from the FAERS database that calculates ROR and PRR values.[18]

The effectiveness of migraine treatment in clinical practice is assessed by looking at factors such as the monthly migraine day count, the percentage change in migraine severity relative to baseline, the need for acute attack drugs, the degree of adverse effects of the drug and patient-reported outcome measures.[19,20] The objective of the present study was to evaluate the "drug ineffective" signaling strength of these drugs through a disproportionality analysis of reports covering all CGRP antagonists used in the treatment of migraine, employing data from an AE reporting system.

## MATERIALS AND METHODS

### Data Source and Collection

In this observational, retrospective pharmacovigilance study, the adverse drug reactions reported in the public version of the FAERS database were used. The medical dictionary for regulatory activities (MedDRA) includes "drug ineffective" as a preferred term (PT).[21] The present study used OpenVigil 2.1-MedDRA-v24 (OpenVigil, Kiel, Germany) to query the FAERS database. Drug ineffective AE reports for the generic name "atogepant", "eptinezumab", "eptinezumab-jjmr", "erenumab", "erenumab-aooe", "fremanezumab", "galcanezumab", "galcanezumab-gnlm", "rimegepant", "rimegepant sulfate", "ubrogepant", "zavegepant" and "zavegepant hydrochloride" have been selected for the period from the last quarter of 2003 to the end of 2024. Adverse reaction reports in which the reporter identified these drugs as "primary suspect" were included in this study.

AE reports of ineffective drugs in the FAERS database were queried for each drug individually using the OpenVigil analysis tool. The association between drug use and AEs was analyzed by selecting "frequency" as the analysis method and "entire cases" as the case type in the query tab of this tool.

### Statistical Analysis

A disproportionality analysis was performed using OpenVigil version 2.1. PRR and ROR were employed to detect safety signals. All algorithms are based on 2×2 contingency tables. In this study, PTs with a reported frequency of ≥3 were selected for the initial screening procedure. ROR and PRR values with a signal strength of 2 or higher were considered as positive signals.[22]

The human-related datasets utilized in this study are available to the public for research purposes. Patient consent was not necessary in this study due to the nature of the data source. The research did not require ethics committee approval because the authors did not participate in data collection or know the participants in the present study.

## RESULTS

### Adverse Event Reports Information

To determine the signal strength of the "drug ineffective" event associated with CGRP antagonists, reports available in the FAERS through December 31, 2024, were included in the study. Of these reports, 11,982 were related to drug inefficacy, with 65.1% (n=7,388) of these reports being related to monoclonal antibodies against CGRP. A greater proportion of the reports was from female patients (59.5%, n=7,135). Among the subsets of reports for which age data were available (6,570 patients without age data), the most common age group was 18-64 years (n=4,381, 36.6%). Most reporters were consumers (n=9,477, 79.1%), with only 20.9% (n=2,500) being healthcare professionals. Details of demographic data related to drug usage are presented in Table 1.

### Disproportionality Analysis Information

After data mining of reports in FAERS, 3,610 reports of small molecule CGRP receptor antagonists and 4,956 reports of monoclonal antibodies against CGRP associated with drug ineffective were found were associated with drug ineffectiveness. In this study, ROR and PRR, were used to analyse AE signals, and 4 potential positive signals were identified from analyzing reports until the end of 2024.

### Small Molecule Calcitonin Gene-Related Peptide Receptor Antagonists

In the current study, rimegepant was found to be the CGRP antagonist with the highest number of reports and signal magnitude (n=3,005, ROR 10.879, PRR 6,708). Other drugs with a positive signal are ubrogepant (ROR 5,865, PRR 4,487) and zavegepant (ROR 3,559; PRR 3,064). Atogepant was found not to generate a positive signal in terms of signal strength (ROR 1,072, PRR 1,067). The results of the disproportionality analysis of small molecule drugs, which block the CGRP receptor, are shown in Table 2.

### Monoclonal Antibodies Against Calcitonin Gene-Related Peptide

Among the monoclonal antibodies against CGRP, only eptinezumab was found to generate a positive signal (ROR 5.7, PRR 4,397). The other drugs, fremanezumab (ROR 1,153, PRR 1,142), galcanezumab (ROR 0,978, PRR 0.98) and erenumab (ROR 0,725, PRR 0,738), had no positive signal strength, although there were reports of drug ineffectiveness events. The results of the disproportionality analysis of monoclonal antibodies against CGRP were shown in Table 3.

## DISCUSSION

To our knowledge, this is the first study on the ineffectiveness of all CGRP antagonist drugs using a large database. Therefore, this study has the potential to be used as a basic resource for future research on the therapeutic ineffectiveness of drugs used in the treatment of migraine.

The results of a recent study demonstrated that consumers were more inclined to report a lack of therapeutic effectiveness than doctors.[6] Similarly, in the present study, a large proportion of those who reported (around four-fifths) were identified as consumers. There is a consensus in the European Headache Federation (EHF) that the evaluation of response to drugs used in migraine treatment should be patient-centred.[23] Considering this information, the report by most consumers that the migraine treatment was ineffective may be considered to increase the value of this study. The study revealed that rimegepant, ubrogepant, eptinezumab, and zavegepant exhibited a positive signal strength for drug ineffectiveness.

One of the most common reasons for discontinuation of small molecule CGRP antagonists is that the drug is ineffective (38%).[24] Ineffectiveness of the drug has also been reported as one of the reasons for switching between drugs in this group.[25] In this study, 36.3% of reports of small molecule CGRP antagonists were found to be ineffective. Compared to other small molecule CGRP receptor antagonists, atogepant had a low rate of ineffectiveness (6.74%) and exhibited no measurable signalling effect.

There are few direct head-to-head studies comparing rimegepant with other migraine treatments[26] and the current study is one of the studies comparing CGRP antagonists with each other. In this evaluation, rimegepant was found to have the highest number of primary suspect cases and the strongest positive signalling strength. In one study, it was determined that most of the patients (69.9%) switched to rimegepant treatment due to the ineffectiveness of other migraine drugs. It was stated that approximately half of the patients in this study (44.9%) were relieved of migraine pain with rimegepant treatment.[27] In a study analysing the data using FAERS data of rimegepant, until the end of the first quarter of 2023, it can be observed that the ROR (14.09) and PRR (10.88) values show a decreasing trend in over 2 years.[28] In this study, it is remarkable that 42.2% of the primary suspect AEs due to rimegepant use were classified as drug ineffective. Although there is a patient population in which rimegepant is effective in studies, it is important to keep in mind that there are patients in whom rimegepant is ineffective; to evaluate this issue during the treatment process and to personalise the treatment.

**Table 1. Basic information on drug ineffectiveness adverse event reports related to CGRP antagonists***

| | | Small molecule CGRP receptor antagonist | | | | Monoclonal antibodies against CGRP | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Category** | **Number of cases (n)** | **Rimegepant (n=3,344)** | **Ubrogepant (n=626)** | **Atogepant (n=537)** | **Zavegepant (n=87)** | **Erenumab (n=3,545)** | **Eptinezumab (n=1,619)** | **Galcanezumab (n=1,570)** | **Fremanezumab (n=654)** |
| **Gender** | Female | 1,975 | 383 | 400 | 68 | 2,050 | 831 | 965 | 463 |
| | Male | 305 | 91 | 75 | 6 | 347 | 186 | 212 | 89 |
| | Unknown | 1,064 | 152 | 62 | 13 | 1,148 | 602 | 393 | 102 |
| **Age (years)** | <18 | 7 | - | - | - | 6 | 3 | 1 | 3 |
| | 18-64 | 1,254 | 84 | 103 | 35 | 1,493 | 887 | 312 | 213 |
| | 65-84 | 249 | 19 | 20 | 3 | 258 | 196 | 82 | 105 |
| | ≥85 | 10 | 2 | 1 | 49 | 8 | 3 | 4 | 2 |
| | Not specified | 1,824 | 521 | 413 | 0 | 1,780 | 530 | 1,171 | 331 |
| **Reporter type** | Healthcare professional | 426 | 121 | 49 | 42 | 1,188 | 297 | 256 | 121 |
| | Consumer | 2,917 | 505 | 488 | 45 | 2,355 | 1,322 | 1,313 | 532 |
| | Not specified | 1 | - | - | - | 2 | - | 1 | 1 |
| **Report year** | 2018 | - | - | - | - | 643 | - | 7 | 16 |
| | 2019 | - | - | - | - | 866 | - | 331 | 157 |
| | 2020 | 250 | 72 | - | - | 696 | 24 | 442 | 73 |
| | 2021 | 739 | 139 | 2 | - | 271 | 192 | 320 | 100 |
| | 2022 | 1,352 | 235 | 261 | - | 235 | 365 | 248 | 106 |
| | 2023 | 578 | 146 | 224 | 37 | 253 | 456 | 115 | 92 |
| | 2024 | 425 | 34 | 50 | 50 | 581 | 582 | 107 | 110 |

*The Food and Drug Administration Adverse Event Reporting System public dashboard was used when preparing this table. Active substances are ranked according to the total number of reports.

CGRP: Calcitonin gene-related peptide.

**Table 2. Disproportionality analysis information of small molecule CGRP receptor antagonist reported to cause drug ineffective***

| Drugs | Total reports (n) | Reports (n) | ROR | 95% CI | PRR | $\chi^2$ | DE/D (%) |
|---|---|---|---|---|---|---|---|
| **Rimegepant** | 7,117 | 3,005 | 10.879 | 10.378; 11.403 | 6,708 | 15515.929 | 42.22 |
| **Ubrogepant** | 1,709 | 484 | 5,865 | 5,279; 6,516 | 4,487 | 1395.609 | 28.32 |
| **Zavegepant** | 367 | 71 | 3,559 | 2,747; 4,612 | 3,064 | 103.178 | 19.35 |
| **Atogepant** | 742 | 50 | 1,072 | 0,805; 1,429 | 1,067 | 0.16 | 6.74 |

*The information in this table was analysed using the OpenVigil tool. It is widely accepted that a chi-square value exceeding 4 is statistically significant.
CI: Confidence interval, $\chi^2$: Chi-squared with Yates', D: Drug, DE: Both the drug was used, and the event occurred, PRR: Proportional reporting ratio, ROR: Reporting odds ratio, CGRP: Calcitonin gene-related peptide.

**Table 3. Disproportionality analysis information of monoclonal antibodies against CGRP reported to cause drug ineffective***

| Drugs | Total reports (n) | Reports (n) | ROR | 95% CI | PRR | $\chi^2$ | DE/D (%) |
|---|---|---|---|---|---|---|---|
| **Eptinezumab** | 5,407 | 1,499 | 5.7 | 5.37; 6.05 | 4,397 | 4187.718 | 27.72 |
| **Fremanezumab** | 7,007 | 505 | 1,153 | 1,053; 1,262 | 1,142 | 9,301 | 7.21 |
| **Galcanezumab** | 21,728 | 1,344 | 0,978 | 0,926; 1,034 | 0.98 | 0,586 | 6.19 |
| **Erenumab** | 34,500 | 1,608 | 0,725 | 0,689; 0,762 | 0,738 | 159.536 | 4.66 |

*The information in this table was analysed using the OpenVigil tool. It is widely accepted that a chi-square value exceeding 4 is statistically significant.
CI: Confidence interval, $\chi^2$: Chi-squared with Yates', D: Drug, DE: Both the drug was used, and the event occurred, PRR: Proportional reporting ratio, ROR: Reporting odds ratio, CGRP: Calcitonin gene-related peptide.

In this study, 7.2% of the reports of the monoclonal antibodies against CGRP drugs were reported as primary suspect due to drug ineffectiveness. According to a few studies conducted in recent years, the ineffectiveness rate in patients receiving monoclonal antibodies against CGRP therapies (except eptinezumab) was 20.3% (n=472); 21.3% (n=169); and 23.2% (n=281).[10,29,30] In the present study, the total number of cases with "drug ineffective" AEs are higher than these studies. However, the total number of AEs reported is also quite high. It might be considered that the presence of eptinezumab in this study and the fact that the main data source is a large database might result in proportional differences. Despite these differences, the main indication of these studies is that monoclonal antibodies against CGRP may be effective in at least three quarters of patients.

A meta-analysis of four randomized controlled trials found that eptinezumab showed excellent efficacy and low side effects in the treatment of migraine.[31] Real-world data on the use of eptinezumab are limited. However, approximately one-third of patients who switched to eptinezumab due to treatment failure after treatment with monoclonal antibodies against CGRP, (erenumab, galcanezumab, fremanezumab) experienced ≥30% reduction in monthly migraine days, while no patient achieved ≥75%.[32] According to the present study, 27.72% of the adverse effects of eptinezumab were due to drug ineffectiveness, and it was found that it ranked 2nd among CGRP monoclonal antibodies in terms of the number of reports. In contrast to eptinezumab, other CGRP monoclonal antibodies had effectiveness that was inversely proportional to the number of cases, and they did not generate positive signal strength. This study shows that eptinezumab is the only drug that has ineffective signalling power among monoclonal antibodies against CGRP. It is recommended to pay attention to this feature of eptinezumab, when switching between these drugs within the same class. In one study, it was shown that the effect of eptinezumab was less in patients who had CGRP antagonist in previous treatment, when patients who used and discontinued monoclonal antibodies against CGRP due to ineffectiveness and similar reasons were compared with patients who did not use the antagonist.[33] Several studies support the recommendation to switch to a second CGRP antagonist monoclonal antibody in the event of an ineffective response to the first CGRP antagonist monoclonal antibody.[34-36] However, there is currently insufficient evidence on the potential benefits of switching from CGRP drugs to monoclonal antibodies.

In the current study, erenumab was found to have the lowest signalling strength, despite having the highest number of ineffectiveness reports, after rimegepant. In many studies, patients who switched to erenumab due to drug ineffectiveness were reported to benefit from erenumab; these findings support the results of our study.[37,38]

The ineffectiveness of drugs used in migraine should be carefully evaluated. Poor efficacy of migraine drugs, especially in the acute treatment of migraine, may lead to progression of migraine.[39,40] The EHF has published a consensus on recommended doses and durations to be used in the assessment of drug ineffectiveness.[41] The concepts of effective and ineffective for the use of triptans as migraine-specific acute treatment are defined by the EHF.[23] Migraine drugs, which are newer than triptans, may also need clearer definitions of ineffectiveness.

### Study Limitations

This study has several limitations. The study was limited to reports in which CGRP antagonist drugs were the primary suspect. The study is limited to reports where "drug ineffective" PT was selected. No restrictions were imposed on the therapeutic indication of the drugs during data analysis; such as for episodic migraine or chronic migraine. There is no information about the duration of drug use in this study. This is an important limitation, especially because of late response to monoclonal antibodies.[42] A causal relationship between the ineffectiveness of these drugs and their intended outcomes could not be established. Although MedDRA is used to code AEs in FAERS, no single

naming scheme is used for drugs. While it is stated that this process is performed automatically in OpenVigil version 2.0.2, it is also noted that some raw FAERS data may be discarded when no drug name can be reccognized.[43] Additionally, this study cannot provide information on the number of reports excluded from evaluation during data mining with OpenVigil, i.e., duplicate or incomplete reports. Despite these limitations inherent in pharmacovigilance studies, spontaneous reporting systems are valuable, as they allow the use of large amounts of data for the safety assessment of potential AEs.

## CONCLUSION

The availability of CGRP antagonists is important to ensure effective treatment for people affected by migraine. Nevertheless, it should be remembered that there have been some reports suggesting that these drugs, which began to be prescribed after erenumab was licensed in 2018, are ineffective. The evaluation of the ineffectiveness of CGRP antagonists provided by this study needs to be supported by other studies that are conducted in the clinic. Given the ineffectiveness of monoclonal antibodies against CGRP in certain patients and the associated financial burden, it would be advantageous for healthcare professionals and patients to be aware of the findings presented in this study.

### MAIN POINTS

- Reports of "drug ineffective" among post-marketing reports play a crucial role in ensuring pharmacovigilance.
- Recognition of drug ineffectiveness in migraine treatment is one of the main conditions that shape treatment.
- There are many "drug ineffective" reports for the eight calcitonin gene-related peptide antagonist drugs used in migraine treatment.
- This study has shown that half of this group of drugs positive signalled "drug ineffective".

### ETHICS

**Ethics Committee Approval:** The research did not require ethics committee approval because the authors did not participate in data collection or know the participants in the present study.

**Informed Consent:** Due to the nature of the data source, patient consent was not obtained in this study.

### DISCLOSURES

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