Real-World Effectiveness of Calcitonin Gene–Related Peptide-Binding Monoclonal Antibodies for Migraine Prevention: A Systematic Review

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ABSTRACT

Background: Migraine is a neurological disease with a high incidence. The new anti-calcitonin gene-related peptide monoclonal antibodies (anti-CGRP mAbs) have demonstrated effectiveness in preventing episodic and chronic migraine.

Objective: To collect evidence of the real-world effectiveness of anti-CGRP mAbs by assessing outcomes such as reduction in monthly migraine days (MMDs), reduction in monthly headache days (MHDs), and percentage of patients having a 50% reduction in MMDs.

Data Sources: The PubMed database was searched for the period from inception to October 20, 2021.

Study Selection and Data Extraction: Of interest for this review were studies that evaluated the real-world effectiveness of anti-CGRP mAbs in terms of MMDs and reduction in MHDs. The search terms included "migraine", "monthly migraine days", and various drug names. The data are reported in terms of patients' baseline characteristics and treatment effectiveness.

Data Synthesis: A total of 46 studies were evaluated, of which 30 (enrolling a total of 4273 patients across 10 countries) were included in the systematic review. The greatest absolute reduction in MMD was from 20.4 at baseline to 10.7 after 3 months of treatment. After 6 months, the greatest absolute difference was 10, relative to baseline. The largest absolute reduction in MHD at 3 months was from 22 to 8, whereas at 6 months, the greatest absolute reduction in MHD was 13. The treatment could be considered clinically effective (≥ 50% reduction in MMDs) for 41% of patients at 3 months and about 44% of patients at 6 months.

Conclusions: Despite substantial variability in baseline values, this review confirmed the effectiveness of anti-CGRP mAbs, which yielded important clinical reductions in both MMDs and MHDs.

Keywords: anti-CGRP mAbs, migraine, effectiveness, real-life, prevention

RÉSUMÉ

Contexte : La migraine est une maladie neurologique à incidence élevée. Le nouvel anticorps monoclonal qui se lie au peptide lié au gène de la calcitonine (AcM anti-CGRP) a démontré son efficacité pour prévenir les migraines épisodiques et chroniques.

Objectif : Recueillir des éléments probants concernant l'efficacité réelle des AcM anti-CGRP en évaluant des résultats comme la réduction du nombre de jours de migraine par mois (JMM), la réduction du nombre de jours de céphalées par mois (JCM) ainsi que le pourcentage de patients ayant une réduction de 50 % du nombre de JMM.

Sources des données : La base de données PubMed a été utilisée pour mener une recherche pour la période allant du début jusqu'au 20 octobre 2021.

Sélection des études et extraction des données : Les auteurs de la revue se sont intéressés aux études qui avaient évalué l'efficacité réelle des AcM anti-CGRP en termes de réduction du nombre de JMM et du nombre de JCM. Les termes de recherche comprenaient « migraine », « jours de migraine par mois » et divers noms de médicaments. Les données sont rapportées en termes de caractéristiques de base des patients et d'efficacité du traitement.

Synthèse des données : Au total, 30 des 46 études répondant aux critères d'inclusion (comprenant un total de 4273 patients dans 10 pays) ont été retenues pour la revue systématique. La réduction absolue de JJM la plus importante était de 20,4 (la base de référence) à 10,7 après 3 mois de traitement. Après 6 mois, la différence absolue la plus importante était de 10 par rapport à la base de référence. La réduction absolue de JCM la plus importante à trois mois était de 22 à 8, alors qu'à 6 mois, la réduction absolue de JCM la plus importante était de 13. Le traitement pouvait être considéré comme cliniquement efficace (≥50 % de réduction de JMM) pour 41 % des patients à 3 mois et environ 44 % des patients à 6 mois.

Conclusions : Malgré la variabilité importante des valeurs de la base de référence, cet examen confirme l'efficacité des AcM anti-CGRP, qui ont donné lieu à une réduction importante d'un point de vue clinique du nombre de JMM et de JCM.

Mots-clés : anticorps monoclonal qui se lie au peptide lié au gène de la calcitonine, anti-CGRP mAbs, AcM anti-CGRP, migraine, efficacité, réalité, prévention

INTRODUCTION

Migraine is a chronic, evolutive neurological disease that affects more than 10% of the population worldwide, with a frequency of occurrence of at least 4 days/month.[1,2] Migraine affects young, mostly female patients, with impacts during their more productive and socially active life years, through disabling episodes that are often inadequately managed by acute medications.[1,3] Until 2019, the pain phase of migraine was exclusively treated with a combination of analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), serotonin receptor agonists, and other classes of drugs such as β-blockers, antidepressants, antiepileptics, and onabotulinum toxin A.[4,5] Although these front-line drugs are used worldwide for the prevention of both chronic and episodic migraine, clinical trials have highlighted a high risk of medical overuse after the use of acute medications.[5-7] With episodic migraine, symptoms occur up to 14 days per month, whereas with chronic migraine, symptoms occur for at least 15 days per month for 3 successive months.

Medical overuse is defined as the excessive use of symptomatic drugs, which are medicinal products that act exclusively on symptoms of the disease, eliminating or attenuating the symptoms for the period of the pharmacological effect, without acting upon the underlying disease itself. In patients with migraine, the risk of medical overuse is very high, especially for drugs such as NSAIDs and corticosteroids, widely used anti-inflammatories that are prescribed as symptomatic remedies. After the entry onto the market of new monoclonal antibodies (mAbs) designed to block signalling of the calcitonin gene–related peptide (CGRP) receptor (specifically erenumab[8,9]) and the anti-CGRP ligand (namely galcanezumab,[10,11] fremanezumab, and eptinezumab[12,13]), recent randomized controlled trials have generated new evidence. These new anti-CGRP mAbs offer major efficacy in the prevention of both episodic and chronic migraine without risk of medical overuse. In particular, anti-CGRP mAbs significantly reduced both monthly migraine days (MMDs) and monthly headache days (MHDs), 2 parameters used to calculate and evaluate the reduction in frequency of migraine.[14,15] MHD refers to the number of days per month on which the patient experiences generic head pain, and MMD refers to the number of days per month on which the patient experiences migraine, a particular type of headache characterized by usually unilateral pain that lasts from 4 to 72 hours and is accompanied by neurovegetative signs and symptoms such as nausea, vomiting, photophobia, and phonophobia.[14,15]

The clinical use of erenumab, galcanezumab, fremanezumab, and eptinezumab is currently authorized in Europe and the United States for patients having at least 4 migraine attacks per month; the anti-CGRP mAbs must be prescribed in a recognized headache centre and are administered at home by a monthly subcutaneous or IV injection.[2,16] In response to the entry of anti-CGRP mAbs onto the Canadian market, this study was conducted with the aims of collecting evidence from the peer-reviewed, published scientific literature regarding the effectiveness of these medications; systematically reviewing their clinical effectiveness, as supported by data collected in the real world; analyzing and evaluating parameters such as reduction in MMDs, reduction in MHDs, and percentage of patients with a reduction in MMDs of about 50%; and comparing and summarizing the most recent clinical studies that have collected real-world data. It is well known that most randomized controlled trials are performed under relatively ideal conditions, which increases the need to demonstrate the effectiveness of new therapies applied to patients not enrolled in any clinical trials, once these therapies have reached the market.[17]

METHODS

This systematic review was carried out in accordance with the PRISMA 2020 statement guidelines[18] and was registered in the PROSPERO database (CRD42021269084). One of the authors (R.L) performed the literature research in the PubMed database (US National Library of Medicine), using the query "(Headache OR Migraine) AND (erenumab OR fremanezumab OR galcanezumab OR eptinezumab) AND ((monthly migraine days) OR (mean change of days) OR (response rate) OR (headache intensity))" on October 20, 2021. All real-world studies analyzing the effectiveness of erenumab, fremanezumab, galcanezumab, or eptinezumab were included in the systematic review. The inclusion criteria envisaged for this study were the conduct of a real-world investigation involving patients experiencing migraine, treatment with at least one of the prespecified anti-CGRP mAbs of interest, measurement of drug effectiveness through outcomes such as MMD or MHD, and follow-up of at least 3 months of treatment. We excluded clinical trials, clinical trial reviews and pooled analyses, purely economic analyses, evaluations of outcomes different from those indicated, studies that assessed only the safety profile of anti-CGRP mAbs, and guidelines.

From each study identified in the database search, the following data were extracted: author and publication year, type of pharmacological treatment, number of patients enrolled, follow-up (i.e., duration of treatment), inclusion and exclusion criteria, previous treatments, country where study was conducted, study design, sponsorship, and outcomes assessed (MMD and/or MHD). After the initial extraction of studies, 2 of the authors (A.Z., R.L.) screened the articles according to the inclusion and exclusion criteria for our systematic review.

The results are expressed descriptively, highlighting baseline characteristics and the effectiveness of treatment as reported in the individual studies. To determine the risk

of bias, study quality was evaluated according to items in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies[19]; for each checklist item, quality was categorized as low, low-medium, medium, medium-high, or high.

RESULTS

Of the 201 articles initially identified, the full text was evaluated for 46, of which 30 were considered for the descriptive analysis (i.e., systematic review; Figure 1).[20-49] These 30 studies enrolled a total of 4273 patients across 10 countries. The results are reported and summarized in Table 1.

The included studies were heterogeneous in terms of study design and other details. The drug eptinezumab was ultimately excluded from the systematic review because no studies investigating administration of this drug in the real-world setting were published at the time of our database search. Overall, 17 (57%) of the 30 studies collected data retrospectively, and 12 (40%) collected data prospectively; only 1 study was a case series. In terms of the study setting, 17 (57%) of the 30 studies were carried out in multiple centres, whereas 13 (43%) were conducted in a single centre. The sample size was highly variable, ranging from a low of 17 patients in the case series of Toni and others[20] to 993 patients in the retrospective review by Faust and others.[21] Consequently, the baseline characteristics of patients were also highly variable. The inclusion and exclusion criteria of individual studies differed substantially. The MMD at baseline ranged from 9.42 in patients affected by episodic migraine, as reported by Scheffler and others,[22] to 27.6, as described by Toni and others.[20] The MHD ranged from 10.4 in patients with episodic migraine in the study by Scheffler and others[22] to 27.3 in the study by Alex and others.[23] The average number of previously failed treatments ranged from 1.4 in the study by Alex and others[23] to 11.2 in that of Robblee and others.[24] In all studies, mAbs were shown to be effective, resulting in substantial reductions in MMD and MHD, relative to baseline. Details of the 30 studies in the systematic review are presented in Supplement 1 (available from https://www.cjhp-online.ca/index.php/cjhp/article/view/3382/).

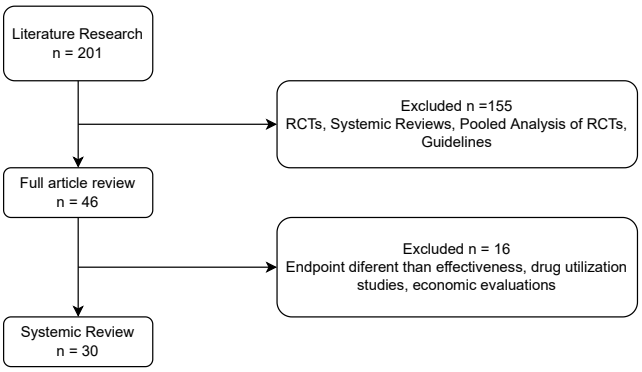

FIGURE 1. Study flow chart.

Five (17%) of the 30 studies showed a low risk of bias, 7 (23%) showed a low–medium risk of bias, 11 (37%) showed a medium risk of bias, 6 (20%) showed a medium–high risk of bias, and 1 showed (3%) a high risk of bias (Supplement 1). The detailed results of the risk-of-bias analysis are available by request to the corresponding author.

Outcomes at 3 Months

The greatest absolute reduction in MMD was observed by Cheng and others,[25] who found that MMD declined from 20.4 at baseline to 10.7 after 3 months of treatment (absolute difference 9.7). By contrast, the smallest absolute reduction in MMD was observed by de Vries Lentsch and others,[26] from 14 to 10.2 (absolute difference 3.8).

The greatest reduction in MHD was observed by De Luca and others[27] (from 22 to 8, absolute difference 14), whereas the smallest reduction was observed by Scheffler and others[22] (from 10.4 to 7.1, absolute difference 3.3, for patients with episodic migraine).

Outcomes at 6 Months

Cheng and others[25] reported the greatest change in MMD at 6 months (absolute difference of 10, relative to baseline), whereas de Vries Lentsch and others[26] reported a smaller change (absolute difference of 9.2, relative to baseline).

In the studies of both De Luca and others[27] and Vernieri and others,[28] the absolute reduction in MHD was 13, starting from baseline values of 22 and 20, respectively. The smallest reduction in MHD was 4.3, noted by Alex and others.[23]

Response to Treatment

Overall, about 41% of patients achieved a reduction in MMD of at least 50% by 3 months, but the values for

TABLE 1. Characteristics of Included Studies and Main Results

Characteristic	No. (%) of Studies or Range of Data (*n* = 30)
Study design	
Retrospective	17 (57)
Prospective	12 (40)
Case series	1 (3)
Single centre	17 (57)
Multiple centres	13 (43)
Summary of results	
Monthly migraine days	
Baseline	9.4–27.6
After 3 months	5.9–22.5
After 6 months	3.0–23.0
Monthly headache days	
Baseline	10.4–27.3
After 3 months	7.1–22.5
After 6 months	7.5–23.0

individual studies were highly variable, ranging from 25% in the study by Scheffler and others[22] to 59% in the study by Cheng and others.[25] At 6 months, about 44% of patients had a response to treatment, with values ranging from 35% in the study by Robblee and others[24] to 50% in the study by Caronna and others.[29]

The values of 41% and 44% reported above represent weighted averages at 3 and 6 months, respectively. For patients with a response at 3 months, the calculation was based on 7 studies (with a total of 1561 patients) that reported this outcome, whereas for patients with a response at 6 months, the calculation was based on 6 studies with a total of 626 patients.

DISCUSSION

The new anti-CGRP mAbs have been on the market only for the past few years, so there is as yet little evidence regarding their effectiveness in the real world, where patients affected by migraine present various clinical characteristics.[15,50] We aimed to collect and compare the data available so far, albeit with certain recognized limitations.

Overall, despite important variability in baseline values, the results of our study confirmed the effectiveness of erenumab, galcanezumab, and fremanezumab in the prevention of chronic and episodic migraine, with substantial reductions in both MMD and MHD. More specifically, patients' MMD declined by about half at both of the prespecified follow-up times (3 and 6 months). Notably, the average MMD did not change substantially from 3 to 6 months, with an absolute change of about 1 day (from 6.3-day reduction at 3 months to 7.7-day reduction at 6 months). Similarly, the average reduction in MHD increased from 7.4 days at 3 months to 8.8 days at 6 months.

There were important differences between the 2 studies that provided data for both 3 and 6 months (Cheng and others[25] and De Vries Lentsch and others[26]) which accounted for MMD data at extremes of the range; these differences can be attributed to the more rigid inclusion criteria used by de Vries Lentsch and others,[26] such as the minimum number of monthly attacks and the specific indication in relation to number of previous treatments. Similarly, the study by Scheffler and others,[22] with a greater number of patients and analysis of MHD at 3 months, was characterized by more rigid inclusion criteria than the study by De Luca and others[27]; this confirms that for studies with different baseline characteristics, the end points may also differ.

We found data confirming the outcome in terms of percentage of "responders" at the 2 specified follow-up times, with about 41% and 44% of patients achieving a reduction in MMD of at least 50% at 3 and 6 months, respectively. It is important to highlight that for this outcome as well, the results of individual studies differed considerably, because of different baseline characteristics and degree of range or rigidity in inclusion criteria.[22,24,25,29] The outcomes also varied according to the country where each study was conducted.[2,29,31,50,51] Therefore, focusing on initial data from published research reinforces the opinion that further data collection is warranted, in more overlapping and comparable clinical contexts, with larger samples of treated patients, to strengthen the reliability of real-world data. Furthermore, to fully determine the impact of anti-CGRP mAbs on the market, it will be necessary and appropriate to consider other factors beyond effectiveness, such as safety and purchase costs, parameters that can affect the administration of these drugs in the real-world context. In particular, the literature still lacks budget impact analyses rating the anti-CGRP mAbs; as such, it is desirable to widen and deepen both the study of effectiveness and safety and the health policy evaluations of these medicinal products in daily clinical practice.

Limitations

This review had several limitations. First, we used a single bibliographic database, which may have led to the omission of some papers not included in the database, as well as other unavoidable omissions that may have occurred despite effective methodology. Second, the extracted studies varied widely in terms of sample size; although this variation did not hinder our comparisons among the studies, it will be essential to extend future investigations to larger samples, since it is desirable to obtain further real-world data to provide new knowledge and insight about these treatments. Third, we considered follow-up over periods of 3 and 6 months, and were unable to carry out longer-term evaluations. As such, it will be necessary in the future to measure the effectiveness of these treatments over longer periods. In fact, with either larger samples or longer follow-up periods, it will be desirable to analyze more data that may further support the effectiveness of anti-CGRP mAbs. Fourth, the high variability in patients' baseline values of both MMD and MHD and the number of previous treatments that patients received before the administration of anti-CGRP mAbs are noteworthy. This aspect can be mostly attributed to either the differing inclusion criteria of the selected studies or the differing admission criteria that regulate the marketing of anti-CGRP mAbs in different countries.[3-5,29,31,50,51] Finally, we limited our analysis to descriptive methods, excluding a quantitative analysis because of the high heterogeneity of the data collected.

CONCLUSION

Our investigation has shown that the marketing of new anti-CGRP mAbs has profoundly influenced the quality of life of patients with migraine, confirming the effectiveness and tolerability of these medicines. This study can be seen as representing a promising starting point. It will be

crucial to pursue in depth, and further extend, the knowledge gained from this systematic review to a larger patient population with broader follow-up, as more real-world data become available. Indeed, with increased reliability of real-world data, and considering that such data continue to offer the most important support for the evidence produced by clinical trials,[52] it will be possible to apply our findings to daily clinical practice and see a markedly improved quality of life in our patients.[53]

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