Original Article

Anti-CGRP mAbs for the Preventive Treatment of Migraine: An Overview Review and a Cost Saving Analysis in the Global Scenario

Hospital Pharmacy
1–8

DOI: 10.1177/00185787231196763
journals.sagepub.com/home/hpx
Sage

Andrea Zovi[1*], Ruggero Lasala[2], Francesco Ferrara[3*], Roberto Langella[4], Antonio Vitiello[5*], Michela Sabbatucci[5], and Umberto Maria Musazzi[6]

Abstract

Objectives: Migraine is a neurological disease with a high frequency of incidence. The new monoclonal antibodies selective for the calcitonin gene-related peptide and its ligand (anti-CGRP mAbs) have been marketed both in the USA and EU based on the positive efficacy results in the prevention of migraine. This search has been carried out with the aim of collecting real-world evidence on the effectiveness of anti-CGRP mAbs, performing a cost-savings analysis, and comparing performances among anti-CGRP mAbs medicines marketed in the American and European market. **Methods:** The literature review has been performed in PubMed database on 31 December 2022; the cost of the unitary dose of anti-CGRP mAbs has been extracted consulting an American national database. **Results:** The results confirm efficacy and good tolerability of anti-CGRP mAbs, determining a difference in the purchase price. In fact, all extracted studies showed a protective risk factor exposure in monthly migraine days reduction for all the anti-CGRP mAbs, whereas the cost analysis showed that using eptinezumab, in a quarter there is a cost saving of at least $425 per patient, compared with the other anti-CGRP mAbs. **Conclusions:** With equal efficacy and equal safety, anti-CGRP mAbs should be prescribed also regard to the cost established at the negotiation, making sure to guarantee the best treatment to the patients, but at the same time impacting as little as possible to the healthcare services resources.

Keywords
migraine, anti-CGRP mAbs, cost, effectiveness, saving, erenumab, galcanezumab, fremanezumab, eptinezumab

Introduction

Migraine is a chronic, evolutive, neurological disease which affects more than 10% of people worldwide, affecting mostly young, female patients, impacting during their more productive, and socially active life years.[1,2] Many adults with migraine or severe headaches are at a disadvantage. In recent years in the United States, migraine has caused an average of about 4 million clinic visits per year, and more than 4 million outpatient visits. In 2018, for example, about 40% of U.S. adults with migraine were unemployed.[3] According to the Global Burden of Disease estimates (GBD) 2019, migraine alone was second among the causes of disability, and first among women under 50 years of age.[4] Until 2019, the pain phase of migraine was treated exclusively with a combination of analgesics such as non-steroidal anti-inflammatory drugs, triptans or other classes of medicines.[5,6] Because of lack of adherence, occurrence of adverse events, and a high risk of developing a medical overuse, there was a loss of beneficial sustain on these treatments.[7] Recently, new monoclonal antibodies (mAbs) designed to block the signaling of the calcitonin gene-related peptide (CGRP), that is, galcanezumab, and its CGRP ligand (ie, erenumab, fremanezumab, and eptinezumab), have been proposed based on pivotal trials. The anti-CGRP mAbs demonstrated their major effectiveness in the reduction of the monthly migraine

[1]University of Camerino, Camerino, Italy
[2]Local Health Unit of Bari, Bari, Italy
[3]Asl Napoli 3 Sud, Nola, Naples, Italy
[4]Agency for Health Protection of the Metropolitan Area of Milan, Milan, Italy
[5]Ministry of Health, Rome, Italy
[6]University of Milan, Milan, Italy

*These authors contributed equally to this work.

Corresponding Author:
Andrea Zovi, School of Pharmacy, University of Camerino, Via Sant'Agostino 1, Camerino 62032, Italy.
Email: zovi.andrea@gmail.com

days (MMD) in comparison to traditional treatments, in the prevention of both episodic migraine (EM) and chronic migraine (CM), without developing a medical overuse and avoiding adverse events.[8-11] CGRP is a neuropeptide which modulates the nociceptive signal: it is a vasodilator that has been associated with the pathophysiology of migraine, as a significant increase of CGRP levels was observed during migraine attack.[12] Nowadays in both the United States of America (USA) and in the European Union (EU) the clinical use of anti-CGRP mAbs has been authorized respectively by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), following a centralized procedure.[13,14] The anti-CGRP mAbs are indicated in patients having at least 4 migraine attacks per month, and the administration must be prescribed in a Headache Center, took via a monthly intravenous injection (eptinezumab) or at home by a subcutaneous administration (erenumab, galcanezumab, fremanezumab).[15] In the USA, both the phases of authorization of new medicinal products and the determination of the drug prices come before the placing on the market of the new products, which are immediately available to the clinical structures and pharmacies.[16] In the EU, after the issue of centralized marketing authorization (MA) by EMA and the publication on the European Official Journal, a medicinal product is authorized to be marketed throughout the EU.[14,17] However, the real access in clinics to the medicinal product may be delayed at national level of Member States by the pathways for defining reimbursement and prescription status.

Objective

In the absence of pivotal studies which have compared the efficacy of individual anti-CGRP mAbs in comparison to other medicines of the same therapeutic class other than placebo, and in relation to anti-CGRP mAbs placed on the global market with a difference in purchase price, this study has been carried out with the aim of searching the most recent literature for studies that may have compared directly or indirectly the efficacy of anti-CGRP mAbs in clinical practice. We assessed anti-CGRP mAbs cost-saving to provide useful and new evidence which may be applicable during the prescribing evaluation steps, in the relevant clinical setting.

Methods

Search Strategy

An overview of systematic reviews for the purpose of extracting effectiveness data has been performed on December 31, 2022 on PubMed® database, using the following query: *"((erenumab AND fremanezumab) OR (fremanezumab AND galcanezumab) OR (erenumab AND galcanezumab) OR (erenumab AND eptinezumab) OR (galcanezumab AND eptinezumab) OR (fremanezumab AND eptinezumab)) AND ((monthly migraine days) OR (monthly headache days) OR (response rate) OR (reduction rate) OR (disability))."*

Inclusion and Exclusion Criteria

To evaluate anti-CGRP mAbs effectiveness, the following inclusion criteria have been considered in the data analysis: all the studies which considered patients affected by migraine and which focused on anti-CGRP mAbs effectiveness, all the studies which compared the efficacy of at least 2 of the 4 anti-CGRP mAbs measured at a follow up of 3 months, in relation to the first revaluation required by the Summary of Product Characteristics (SPC) of these medicines. In particular, for the evaluation of the effectiveness of the anti-CGRP mAbs we included randomized clinical trials, real world studies, reviews and meta-analyses; case reports have been excluded. All studies which did not examine at least 2 medicinal products between erenumab, fremanezumab, galcanezumab, and eptinezumab have been excluded, as well as all studies which did not investigate MMD as the primary outcome (Figure 1).

Article Selection and Data Extraction

Two reviewers (A.Z. and R.LS.) screened all titles, abstracts and full texts independently, and solved disagreements by consensus or consultation with a third reviewer. Then the following information has been extracted: (i) first author, (ii) year of publication, (iii) type of study, (iv) journal, (v) anti-CGRP mAbs studied, (vi) duration of treatment, (vii) adverse events described, and (viii) efficacy of anti-CGRP mAbs versus placebo. The details are shown in Table 1. The efficacy of the medicinal products compared to the placebo has been assessed in terms of risk ratio. Unit dose cost and dosage regimens of anti-CGRP mAbs have been extracted by consulting Drugs.com, a virtual platform which includes all medicines authorized by the FDA and placed on the American pharmaceutical market.

Data Analysis

We conducted a descriptive analysis of the characteristics of the included literature. The evaluation of the cost analysis has been carried out in accordance with the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS2022) checklist.

Results

Search Results

Overall, we identified 67 studies from the literature search, of which 57 studies were excluded since they did not fall under the inclusion criteria of our study. Ten out of the 67

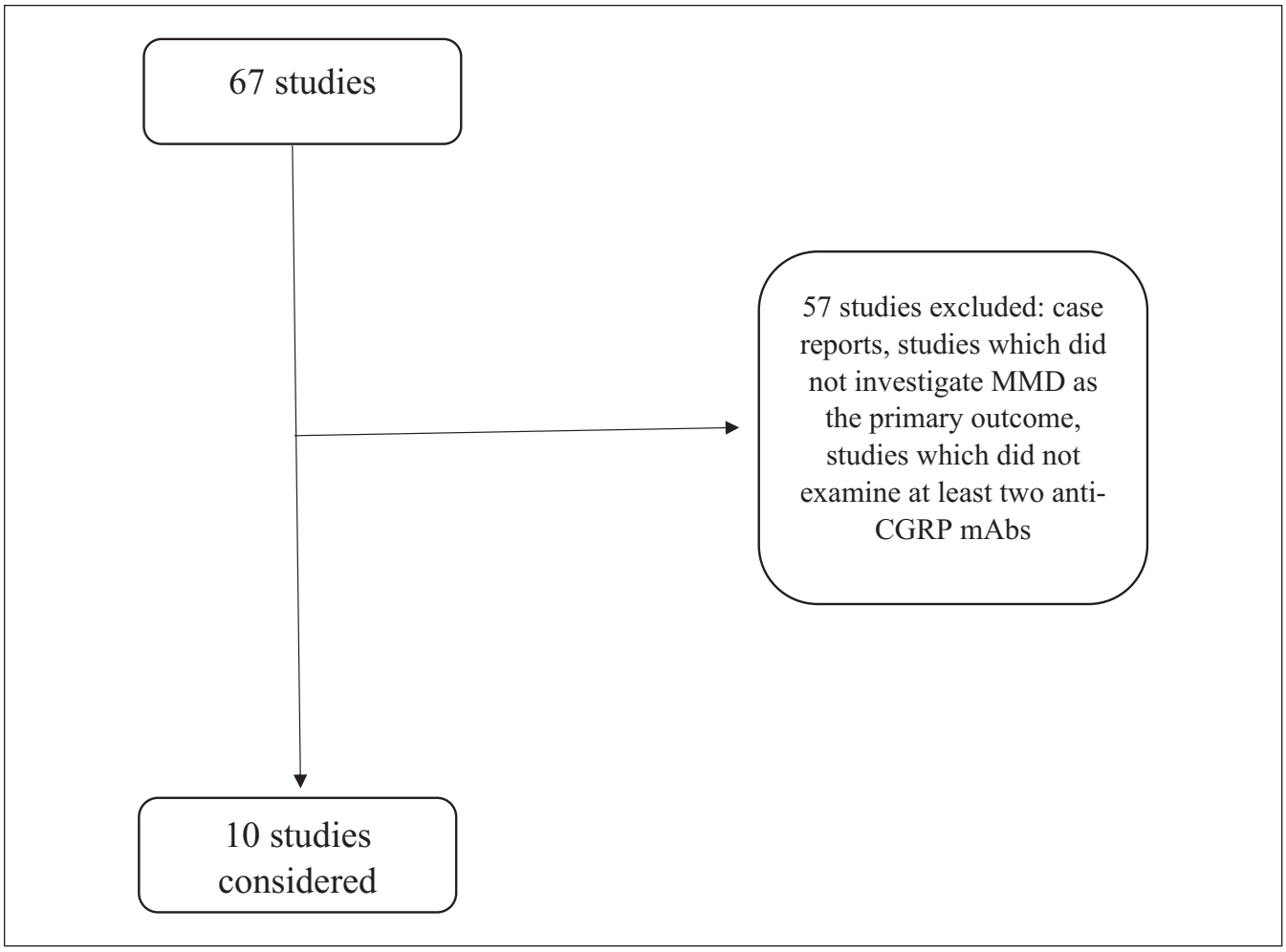

Figure 1. Flow-chart of considered studies.

studies indirectly compared the efficacy of at least 2 anti-CGRP antibodies to each other, but always comparing single anti-CGRP mAbs to placebo and never with head-to-head studies (Figure 1).

Characteristics of Included Articles/Studies

Of the 10 studies included (Table 1), 4 (40%) were systematic review-meta-analysis, 3 (30%) were meta-analysis, 1 (10%) was an observational study, 1 (10%) a comparative study, and 1 (10%) a retrospective real-life study. One article was published in 2018, then none in 2019, 2 in 2020, 4 in 2021, and 3 in 2022.

Effectiveness of Anti-CGRP mAbs

All the 10 studies selected showed a protective exposure to risk factor in MMD reduction: in fact, risk ratio values are in all cases under 0, confirming that the efficacy event—that is, the reduction in the number of monthly migraine days in the group of treated subjects—is higher and significant than in the control group. Similarly, assessing the occurrence of adverse events, the risk ratio value in most cases does not exceed 1, confirming that the risk of the event occurring in the treated group is lower than in the control group (Table 1). Although head-to-head studies between the anti-CGRP mAbs have not been published yet, nor in pivotal trials historical controls with drugs used to treat migraine such as calcium antagonists or botulinum toxin A have been used, currently a major efficacy of 1 anti-CGRP mAb compared to the others has been not demonstrated significantly. However, the comparison was not placed as the main objective of the study, but was developed as a surrogate endpoint.

Cost-Saving Analysis

The cost-saving analysis in the American scenario highlighted eptinezumab as the anti-CGRP mAb with the minor cost, followed by fremanezumab, erenumab, and galcanezumab. In a quarter, the treatment with eptinezumab 100 mg,

Table 1. Literature's Review of the Studies That Compared Effectiveness of anti-CGRP mAbs (Eptinezumab, Erenumab, Fremanezumab, and Galcanezumab) at 12-Week Follow-Up, as of 31 December 2022.

First author of the study	Year of publication	Type of study	Anti-CGRP mAbs studied	Adverse events described (expressed in risk ratio, 95% CI)	Efficacy of anti-CGRP mAbs vs placebo: reduction of MMD in subgroups (expressed in risk ratio, 95% CI)
Deng et al[18]	2020	Systematic review—meta-analysis	Erenumab-Fremanezumab-Galcanezumab	Erenumab: 0.93 (0.85, 1.01) Fremanezumab: 0.99 (0.72, 1.35) Galcanezumab: 1.06 (0.98, 1.14)	Erenumab: −1.27 (−1.61, −0.92) Fremanezumab: −1.99 (−3.23, −0.75) Galcanezumab: −1.57 (−2.03, −1.10)
Wang et al[19]	2021	Systematic review—meta-analysis	Erenumab-Fremanezumab-Galcanezumab	Erenumab: 0.98 (0.88, 1.09) Fremanezumab: 1.05 (0.92, 1.17) Galcanezumab: 1.1 (1.01, 1.22)	Erenumab: −1.61, (−2.40, −0.84) Fremanezumab: −2.19 (−3.15, −1.25) Galcanezumab: −2.10 (−2.76, −1.45)
Masoud et al[20]	2021	Systematic review—meta-analysis	Erenumab-Fremanezumab-Galcanezumab	Not treated	Erenumab: −0.38, (−0.46, −0.30) Fremanezumab: −0.35 (−0.47, −0.24) Galcanezumab: −0.33 (−0.41, −0.25)
Popoff et al[21]	2021	Comparative study	Erenumab-Galcanezumab	Not treated	Erenumab: −0.06 (−0.61, 0.50) Galcanezumab: −0.59 (−0.13, −1.32)
Alasad and Asha[22]	2020	Meta-analysis	Erenumab-Fremanezumab-Galcanezumab	Overall treated for the 3 anti-CGRP mAbs—not considered	Erenumab: −1.59 (−2.06, −1.12) Fremanezumab: −2.23 (−3.36, −1.09) Galcanezumab: −1.79 (−2.23, −1.35)
Viudez-Martínez et al[23]	2022	Observational study	Erenumab-Galcanezumab	Overall treated for the 2 anti-CGRP mAbs—not considered	Erenumab: − 5.05 (−3.03, − 7.07) Galcanezumab: −5.36 (−2.97, −7.75)
Zhu et al[24]	2018	Meta-analysis	Erenumab-Fremanezumab-Galcanezumab	Erenumab: 0.98 (0.87, 1.11) Fremanezumab: 1.00 (0.66, 1.52) Galcanezumab: 1.05 (0.91, 1.22)	Erenumab: −1.63 (−2.31, −0.96) Fremanezumab: −1.83 (−2.55, −1.10) Galcanezumab: −1.10 (−1.18, −1.02)
Chen et al[25]	2021	Systematic review—meta-analysis	Fremanezumab-Galcanezumab	Fremanezumab: 1.17 (1.00, 1.36) Galcanezumab: 1.79 (0.66, 4.88)	Fremanezumab: −0.48 (−0.93, −0.03) Galcanezumab: −0.87 (−1.33, −0.42)
Cantarelli et al[26]	2022	Retrospective real life study	Erenumab-Fremanezumab-Galcanezumab	Suspension by toxicity, n (%) Galcanezumab: Four (9.3) Fremanezumab: 0 (0) Erenumab: Eight (16.7)	Erenumab: 21.9 [7.7]-5 (11.1) Fremanezumab: 14 [4.2]-1 (7.7) Galcanezumab: 20.9 [6.6]-6 (15.8)
Wang et al[27]	2022	Meta-analysis	Erenumab-Fremanezumab-Galcanezumab-Eptinezumab	Erenumab: 0.98 (0.84, 1.13) Galcanezumab: 0.97 (0.81, 1.15) Fremanezumab: 0.97 (0.70, 1.36) Eptinezumab: 1.06 (0.88, 1.29)	Erenumab: −1.81 (−4.02, −0.35) Galcanezumab: −3.09 (−5.03, −1.08) Fremanezumab: −3.5 (−5.95, −0.94) Eptinezumab: −2.7 (−5.21, −0.19)

Note. CGRP = calcitonin gene-related peptide; MMD = monthly migraine days; CI = confidence interval.

Table 2. Cost-Saving Analysis of Medicinal Products Containing Anti-CGRP mAbs Authorized and Marketed in the USA, as of 31 December 2022.

API	Medicinal product	MA date	Strengths	Administration route	Price ex-factory/ unit ($)	Vials administered in a quarter	Quarterly treatment price ($)	Saving Δ ($)
Eptinezumab	Vyepti®	21/02/2020	100 mg/1 mL	IV	1705	1	1705	Basal value
Erenumab	Aimovig®	17/05/2018	70 mg/1 mL	SC	743	3	2229	524
Erenumab	Aimovig®	17/05/2018	140 mg/1 mL	SC	743	3	2229	524
Fremanezumab	Ajovy®	14/09/2018	225 mg/1.5 mL	SC	710	3	2130	425
Fremanezumab	Ajovy®	14/09/2018	675 mg/1.5 mL	SC	2130	1	2130€	425
Galcaezumab	Emgality®	27/09/2018	120 mg/1 mL	SC	697	4	2788	1083

Note. CGRP = calcitonin gene-related peptide; API = active pharmaceutical ingredient; MA = marketing authorization; IV = intravenous; SC = subcutaneous.

fremanezumab 225 mg, fremanezumab 675 mg, erenumab 70 mg, erenumab 140 mg, and galcanezumab 120 mg costs to the national healthcare service $1.705, $2.130, $2.130, $2.229, $2.229, and $2.788, respectively. Consequently, in a quarter there is a cost saving of $425, $524, and $1.083 per patient using eptinezumab, regardless from the dosage, rather than fremanezumab, erenumab, or galcanezumab, respectively. The different costs of eptinezumab, erenumab, galcanezumab, and fremanezumab are illustrated in Table 2. Analyzing only the anti-CGRP mAbs administered subcutaneously, it appears that in one quarter, using fremanezumab, there would be a cost saving per patient respectively of $99 and $658, regardless of dosage, compared with using erenumab or galcanezumab.

Discussion

Our investigation confirms that the marketing of the new anti-CGRP mAbs has profoundly influenced the quality of life of migraine patients, confirming the efficacy and the good tolerability of these medicinal products. In this context, it is noteworthy that, unlike eptinezumab, other anti-CGRP mAbs are indicated for s.c. administration (Table 2). However, significant price gaps among anti-CGRP mAb products have been highlighted. In fact, eptinezumab is the medicinal product with the lowest purchase price, whereas the treatment with galcanezumab costs the most. It is noteworthy that eptinezumab is only administrable e.v. in outpatient settings, therefore, the actual cost of its administration is expected to vary, depending on the actual care costs incurred by the facility in the outpatient settings, as well as with the occurrence of any side effects when the drug is administered. In addition, patients who take eptinezumab often have to switch to the 300 mg formulation to achieve the therapeutic effect, causing a sharp 3-time increase in treatment costs.[28] Furthermore, from our study it emerges that anti-CGRP mAbs are only indirectly compared to each other. Indeed, head-to-head studies, which directly compare the effectiveness and safety among single anti-CGRP mAbs as a primary endpoint, have not been published yet. From our search we noticed that erenumab is the anti-CGRP mAb more prescribed, but we should assume that the reason is not attributable to the lower price of erenumab than galcanezumab or 300 mg eptinezumab, but rather to the fact that it has been marketed both in USA and in Europe at least 1 year before all the other anti-CGRP mAbs.[13,17] In fact, since galcanezumab, fremanezumab, and eptinezumab have also been placed on the market, it seems that physicians tend to equally address the therapeutic choice between all the anti-CGRP mAbs, having to assess several variabilities during the prescription phase such as the availability of the medicines in the clinical setting, the local technical specifications, medicines' shortages, etc.[29] On the other hand, it is noteworthy that the treatment with galcanezumab in a trimester costs the most due to the double vials administered during the induction phase. Migraine has a huge financial burden on global economies, costing $19.6 in the USA[30] and €27 billion[31] in the EU annually. Rather, the true socioeconomic cost of migraine is likely higher than that, given it costs nearly £6 billion in service use and lost employment in the United Kingdom alone.[32] Therefore, economic analysis of new treatments is key to offering the patient the best available treatment while preserving the economic resources of healthcare systems.

Limitations

The studies considered in our analysis assessed the efficacy of the anti-CGRP mAbs at a heterogeneous time follow-up, which in most cases has been estimated at 3 months, but in others at 6 months or even 12 months. In relation to anti-CGRP mAbs efficacy, in our analysis we considered the 3 months period only, as it was the period with the most data available. Probably, this is justified by the fact that most of the studies extracted from our analysis were conducted in the years 2020 to 2021, therefore the time period with respect to patients enrolled was shorter than in studies published more recently. In addition, it is often documented in the literature that the efficacy does not undergo noteworthy changes by lengthening the follow-up time[33-36]: actually, the efficacy at

Table 3. Analysis of Prices of Medicinal Products Containing Anti-CGRP mAbs Authorized in the EU and Marketed in the 2 Main European Markets, as of 31 December 2022.

API	Medicinal product	MA procedure	MA date	Strengths	Administration route	German price ex-factory/ unit (€)	Italian price ex-factory/ unit (€)
Eptinezumab	Vyepti®	Centralized, full application	24/01/22	100 mg/1 mL	IV	1392.65	-
Erenumab	Aimovig®	Centralized, full application	26/07/18	70 mg/1 mL	SC	311.95	383.56
Erenumab	Aimovig®	Centralized, full application	26/07/18	140 mg/1 mL	SC	311.95	383.56
Fremanezumab	Ajovy®	Centralized, full application	28/03/19	225 mg/1.5 mL	SC	444.94	425.00
Fremanezumab	Ajovy®	Centralized, full application	28/03/19	675 mg/1.5 mL	SC	1312.25	1275.00
Galcaezumab	Emgality®	Centralized, full application	14/11/18	120 mg/1 mL	SC	490.33	403.75

Note. CGRP = calcitonin gene-related peptide; API = active pharmaceutical ingredient; MA = marketing authorization; IV = intravenous; SC = subcutaneous.

3 months after the first administration of the drug has similar values to that found at 6 or 12 months of treatment. In regard to the cost-saving analysis, we considered only USA purchase prices for 2 basic reasons. Firstly, the USA is a more mature market than the EU for anti-CGRP mAbs as FDA released its authorization earlier than EMA; secondly, comparing USA prices with those in major European countries (since they are not centrally established in the EU), no noteworthy net differences were found on the euro-dollar currency exchange rate (Tables 2 and 3).

Conclusions

Migraine is the most disabling of all neurological disorders, with an estimated global prevalence of 14.0% (range 12.9%-15.2%). Worldwide, in 2019, migraine was responsible for 42.1 million (95% CI 6.42-95.6) years lived with disability (YLDs), or 4.8% (0.8-10.1) of total YLDs.[37] Migraine headache makes up 88.2% (60.7%-97.7%) of the global burden of headache disorders. Therefore, efficacy and safety profiles being equal, the use of anti-CGRP mAbs in clinical settings should also take into consideration the impact of such treatments on the economic sustainability of healthcare systems and services. Particularly, in the last decades, the mission of healthcare systems has been made increasingly difficult by the rising costs for innovative treatments. Considering the limited economic resources, it is strategic to optimize the therapy prescription in order to identify the most appropriate pharmacological treatment for the patient. Supporting the selection of the most proper treatment with cost-saving data is particularly relevant for treating chronic diseases (eg, migraine) that require long-life treatment. For innovative treatments, hospital pharmacists play an important role in supporting the clinical assessments in setting up pharmacological treatments, collaborating in multidisciplinary teams with the physicians and with the local decision-makers, to be able to carry out the best choices for the patients and for national healthcare system economic resources. This is particularly true for patients affected by CM and EM, which are generally treated in outpatients' settings. It is also notable that recently came into the market the gepant medicines, new therapeutic alternatives for the treatment of migraine prevention administered orally and which may be added to the arsenal of current migraine management. Therefore, it will be desirable to acquire new evidence about safety and efficacy of migraine prevention medicines, to be able to provide more data which may be assessed by the multidisciplinary hospital teams, also to detect differences in the efficacy of anti-CGRP mAbs in patient subgroups.[38]

Author's Note

The authors certify that the manuscript is original, never submitted to other journal for publication before. All authors contributed equally to the manuscript and had the opportunity to revise and approve the final text. All the authors declare that the opinions expressed are of a personal nature and do not in any way commit the responsibility of the Administrations to which they belong.

Acknowledgments

None.

Author Contributions

Andrea Zovi (A.Z.), Francesco Ferrara (F.F.), Ruggero Lasala (R.LS.), Roberto Langella (R.L.), Antonio Vitiello (A.V.), Michela Sabbatucci (M.S.) Umberto Maria Musazzi (U.M.M.). Conceptualization, A.Z., A.V.; methodology, A.Z., R.LS., M.S., U.M.M; investigation, A.Z., F.F.; writing - original draft preparation, A.Z., U.M.; writing - review and editing, R.LS, F.F., R.L., A.V., M.S., U.M.M.; visualization, R.LS, F.F., R.L., A.V., M.S., U.M.M. All the authors have read and agreed to the published version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

Not applicable.

Consent to Participate

Not applicable.

Consent to Publish

The authors consent to the publication of the manuscript.

ORCID iD

Andrea Zovi https://orcid.org/0000-0002-6528-2171

Availability of Data and Materials

Full availability of data and materials.

References

1. Andreou AP, Edvinsson L. Mechanisms of migraine as a chronic evolutive condition. *J Headache Pain*. 2019;20(1):117. doi:10.1186/s10194-019-1066-0
2. Food and Drug Administration [Internet]. Updated May 22, 2018. Accessed February 16, 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-preventive-treatment-migraine
3. Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: updated age, sex, and socioeconomic-specific estimates from government health surveys. *Headache*. 2021;61(1):60-68. doi:10.1111/head.14024
4. Steiner TJ, Stovner LJ, Jensen R, Uluduz D, Katsarava Z. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. *J Headache Pain*. 2020;21(1):137. doi:10.1186/s10194-020-01208-0
5. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and Prevention. *Headache*. 2015;55(Suppl 2):103-122.
6. Al-Quliti KW, Assaedi ES. New advances in prevention of migraine. Review of current practice and recent advances. *Neurosci*. 2016;21(3):207-214. doi:10.17712/nsj.2016.3.20150506
7. May A, Schulte LH. Chronic migraine: risk factors, mechanisms, and treatment. *Nat Rev Neurol*. 2016;12(8):455-464. doi:10.1038/nrneurol.2016.93
8. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;91(24):E2211-E2221. doi:10.1212/WNL.0000000000006640
9. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol*. 2017;16(6):425-434. doi:10.1016/s1474-4422(17)30083-2
10. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med*. 2017;377(22):2113-2122. doi:10.1056/NEJMoa1709038
11. Villar-Martínez MD, Moreno-Ajona D, Goadsby PJ. Eptinezumab for the preventive treatment of migraine. *Pain Manag*. 2021;11(2):113-121. doi:10.2217/pmt-2020-0075
12. Edvinsson L, Warfvinge K. Recognizing the role of CGRP and CGRP receptors in migraine and its treatment. *Cephalalgia*. 2019;39:366-373.
13. Food and Drug Administration [Internet]. Updated November 16, 2022. Accessed February 16, 2023. https://www.fda.gov/drugs/drug-approvals-and-databases/resources-information-approved-drugs
14. European Medicines Agency [Internet]. Marketing authorization. Updated not available. Accessed February 16, 2023. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation
15. Pellesi L, Guerzoni S, Pini LA. Spotlight on anti-CGRP monoclonal antibodies in migraine: the clinical evidence to date. *Clin Pharmacol Drug Dev*. 2017;6(6):534-547. doi:10.1002/cpdd.345
16. Mills M, Michaeli D, Miracolo A, Kanavos P. Launch sequencing of pharmaceuticals with multiple therapeutic indications: evidence from seven countries. *BMC Health Serv Res*. 2023;23(1):150. doi:10.1186/s12913-023-09095-2
17. European Medicines Agency [Internet]. Updated May 16, 2002. Accessed February 16, 2023. https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines
18. Deng H, Li GG, Nie H, et al. Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine - an updated systematic review and meta-analysis. *BMC Neurol*. 2020;20:57. doi:10.1186/s12883-020-01633-3
19. Wang X, Chen Y, Song J, You C. Efficacy and safety of monoclonal antibody against calcitonin gene-related peptide or its receptor for migraine: a systematic review and network meta-analysis. *Front Pharmacol*. 2021;12:649143. doi:10.3389/fphar.2021.649143
20. Masoud AT, Hasan MT, Sayed A, et al. Efficacy of calcitonin gene-related peptide (CGRP) receptor blockers in reducing the number of monthly migraine headache days (MHDs): a network meta-analysis of randomized controlled trials. *J Neurol Sci*. 2021;427:117505. doi:10.1016/j.jns.2021.117505
21. Popoff E, Johnston K, Croop R, et al. Matching-adjusted indirect comparisons of oral rimegepant versus placebo, erenumab, and galcanezumab examining monthly migraine days and health-related quality of life in the treatment of migraine. *Headache*. 2021;61(6):906-915. doi:10.1111/head.14128
22. Alasad YW, Asha MZ. Monoclonal antibodies as a preventive therapy for migraine: a meta-analysis. *Clin Neurol Neurosurg*. 2020;195:105900. doi:10.1016/j.clineuro.2020.105900
23. Viudez-Martínez A, Pascual-Carrasco A, Beltrán-Blasco I, Hernandez-Lorido R, F Ruiz de Apodaca R. Effectiveness and safety of erenumab and galcanezumab in the prevention of chronic and episodic migraine: a retrospective cohort study. *J Clin Pharm Ther*. 2022;47(6):814-823. doi:10.1111/jcpt.13620
24. Zhu Y, Liu Y, Zhao J, Han Q, Liu L, Shen X. The efficacy and safety of calcitonin gene-related peptide monoclonal antibody for episodic migraine: a meta-analysis. *Neurol Sci*. 2018;39(12):2097-2106. doi:10.1007/s10072-018-3547-3
25. Chen YY, Ye XQ, Tang TC, She TW, Chen M, Zheng H. Calcitonin gene-related peptide monoclonal antibodies versus botulinum neurotoxin a in the preventive treatment of chronic migraine:

an adjusted indirect treatment comparison meta-analysis. *Front Pharmacol*. 2021;12:671845. doi:10.3389/fphar.2021.671845
26. Cantarelli L, Pestana Grafiña D, Gonzalez Perez A, et al. Efficacy and safety of erenumab, galcanezumab, and fremanezumab in the treatment of drug-resistant chronic migraine: experience in real clinical practice. *Ann Pharmacother*. 2023;57(4):416-424. doi:10.1177/10600280221118402
27. Wang X, Wen D, He Q, You C, Ma L. Efficacy and safety of monoclonal antibody against calcitonin gene-related peptide or its receptor for migraine patients with prior preventive treatment failure: a network meta-analysis. *J Headache Pain*. 2022;23(1):105. doi:10.1186/s10194-022-01472-2
28. Goadsby PJ, Barbanti P, Lambru G, et al. Eptinezumab improved patient-reported outcomes and quality of life in patients with migraine and prior preventive treatment failures. *Eur J Neurol*. 2023;30:1089-1098. doi:10.1111/ene.15670
29. Zovi A, Musazzi UM, D'Angelo C, Piacenza M, Vimercati S, Cilurzo F. Medicines shortages and the perception of healthcare professionals working in hospitals: an Italian case study. *J Interprof Educ Pract*. 2021;25:100472. doi:10.1016/j.xjep.2021.100472
30. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA*. 2003;290(18):2443-2454. doi:10.1001/jama.290.18.2443
31. Andlin-Sobocki P, Jönsson B, Wittchen HU, Olesen J. Cost of disorders of the brain in Europe. *Eur J Neurol*. 2005;12(Suppl 1):1-27. doi:10.1111/j.1468-1331.2005.01202.x
32. McCrone P, Seed PT, Dowson AJ, et al. Service use and costs for people with headache: a UK primary care study. *J Headache Pain*. 2011;12(6):617-623. doi:10.1007/s10194-011-0362-0
33. Cheng S, Jenkins B, Limberg N, Hutton E. Erenumab in chronic migraine: an Australian experience. *Headache*. 2020;60(10):2555-2562. doi:10.1111/head.13968
34. de Vries Lentsch S, Verhagen IE, van den Hoek TC, MaassenVanDenBrink A, Terwindt GM. Treatment with the monoclonal calcitonin gene-related peptide receptor antibody erenumab: a real-life study. *Eur J Neurol*. 2021;28(12):4194-4203. doi:10.1111/ene.15075
35. Scheffler A, Messel O, Wurthmann S, et al. Erenumab in highly therapy-refractory migraine patients: first German real-world evidence. *J Headache Pain*. 2020;21(1):84. doi:10.1186/s10194-020-01151-0
36. De Luca C, Baldacci F, Mazzucchi S, et al. CGRP inhibitors and oxidative stress biomarkers in resistant migraine: a real-life study with erenumab, fremanezumab, and galcanezumab. *J Clin Med*. 2021;10(19):4586. doi:10.3390/jcm10194586
37. IHME [Internet]. Migraine - level 4 cause. Accessed February 16, 2023. https://www.healthdata.org/results/gbd_summaries/2019/migraine-level-4-cause
38. Noseda R, Bedussi F, Gobbi C, Zecca C, Ceschi A. Safety profile of erenumab, galcanezumab and fremanezumab in pregnancy and lactation: analysis of the WHO pharmacovigilance database. *Cephalalgia*. 2021;41(7):789-798. doi:10.1177/0333102420983292