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Monoclonal antibodies against calcitonin gene-related peptide in chronic migraine: an adjusted indirect treatment comparison

Comparación indirecta ajustada de anticuerpos monoclonales contra el péptido relacionado con el gen de la calcitonina en migraña crónica

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Abstract

Objective: New monoclonal antibodies against the calcitonin gene-related peptide pathway have recently been developed for the prevention of migraine. The aim of this study is to compare the efficacy of monoclonal antibodies against the calcitonin generelated peptide pathway drugs in chronic migraine through an adjusted indirect treatment comparison, and to establish whether they can be considered equivalent therapeutic alternatives in this pathology.

Method: A bibliographic search of randomized clinical trials was performed in PubMed database on December 26, 2019. The inclusion criteria were phase II/III randomized clinical trials of monoclonal antibodies against the calcitonin generelated peptide pathway with similar population, length of follow-up and treatment comparator. The reduction of at least 50% migraine-days/month was selected as efficacy endpoint. Chronic migraine was defined as ≥ 15 headache days/month, of which ≥ 8 were migraine-days (event duration ≥ 4 hours). Randomized clinical trials with different clinical chronic migraine context and definition of disease were excluded. An indirect treatment comparison was developed using Bucher's method. The equivalent therapeutic alternatives positioning guide was used for the evaluation of potentially equivalent alternatives. Delta value (Δ, maximum difference as clinical criterion of equivalence) was calculated as half of absolute risk reduction obtained in

Resumen

Objetivo: Recientemente se han desarrollado anticuerpos monoclonales contra la vía del péptido relacionado con el gen de la calcitonina para la prevención de la migraña. El objetivo de este estudio es comparar la eficacia de los fármacos anticuerpos monoclonales contra la vía del péptido relacionado con el gen de la calcitonina en migraña crónica a través de una comparación indirecta ajustada, y establecer si pueden considerarse alternativas terapéuticas equivalentes en esta patología.

Método: Se realizó una búsqueda bibliográfica de ensayos clínicos aleatorizados en la base de datos PubMed el 26 de diciembre de 2019. Los criterios de inclusión fueron: ensayos clínicos aleatorizados fase II/III de anticuerpos monoclonales contra la vía del péptido relacionado con el gen de la calcitonina con similar población, duración de seguimiento y comparador. Se seleccionó la reducción de al menos un 50% de días de migraña/mes como variable de eficacia. Se definió migraña crónica como ≥ 15 días de dolor de cabeza/mes, de los cuales ≥ 8 fueron días de migraña (duración del evento ≥ 4 horas). Se excluyeron los ensayos clínicos aleatorizados con diferentes contextos clínicos de migraña crónica y definición de enfermedad. Se desarrolló una comparación indirecta ajustada utilizando el método de Bucher. Para la evaluación de la posible equivalencia terapéutica se siguieron las directrices de la guía de alternativas terapéuticas equivalentes de posicionamiento. El valor delta (Δ, máxima diferencia como criterio clínico de equivalencia) se calculó como la

KEYWORDS
Migraine disorders; Calcitonin gene related peptide; Monoclonal antibodies; Evidence based medicine; Neurology.

PALABRAS CLAVE
Trastornos de migraña; Péptido relacionado con el gen de calcitonina; Anticuerpos monoclonales; Medicina basada en evidencia; Neurología.

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a meta-analysis of randomized clinical trials included in indirect treatment comparison.
Results: Thirty randomized clinical trials were found: erenumab (*n* = 12), fremanezumab (*n* = 7), galcanezumab (*n* = 10) and eptinezumab (*n* = 1). Three studies were selected: one of erenumab, one of fremanezumab and another of eptinezumab. The rest were not included in indirect treatment comparison for non-compliance of inclusion criteria. Results of indirect treatment comparison among different regimens of studied drugs showed no statistically significant differences, and the most part of 95% confidence interval was within calculated delta margins (Δ = 9.5%). No relevant safety differences among the three drugs were found.
Conclusions: Indirect treatment comparison showed no statistically significant differences in reduction of ≥ 50% migraine days/month between erenumab, fremanezumab and eptinezumab. Probable clinical equivalence was found between these drugs in terms of efficacy and safety, therefore they could be considered equivalent therapeutic alternatives in chronic migraine.

mitad de la reducción absoluta del riesgo obtenida en un metaanálisis de los ensayos clínicos aleatorizados incluidos en la comparación indirecta ajustada.
Resultados: Se encontraron 30 ensayos clínicos aleatorizados: erenumab (*n* = 12), fremanezumab (*n* = 7), galcanezumab (*n* = 10) y eptinezumab (*n* = 1). Se seleccionaron tres estudios: uno de erenumab, uno de fremanezumab y otro de eptinezumab. El resto no se incluyó en la comparación indirecta ajustada por incumplimiento de los criterios de inclusión. Los resultados de la comparación indirecta ajustada entre las diferentes posologías de los fármacos estudiados no mostraron diferencias estadísticamente significativas, y la mayor parte del intervalo de confianza del 95% se encontró dentro de los márgenes delta calculados (Δ = 9,5%). No se encontraron diferencias de seguridad relevantes entre los tres medicamentos.
Conclusiones: La comparación indirecta ajustada no mostró diferencias estadísticamente significativas en la reducción de ≥ 50% de días de migraña/mes entre erenumab, fremanezumab y eptinezumab. Se encontró una probable equivalencia clínica entre estos fármacos en términos de eficacia y seguridad, por lo que podrían considerarse alternativas terapéuticas equivalentes en migraña crónica.

Introduction

Migraine is a primary headache that occurs as recurrent episodes of pain, of variable duration and moderate-severe intensity. It is usually manifested as unilateral and pulsatile pain, accompanied by nausea, photophobia and phonophobia. In 30% of patients, it is preceded by transient focal neurological symptoms (visual or sensory) called aura[1]. Depending on the frequency of occurrence of episodes, it is classified as episodic migraine (EM, headache less than 15 days per month) and chronic migraine (CM, 15 or more days of headache per month for more than 3 months, of which at least 8 days are migraine days).

This disorder affects approximately 15% of the population, being 2-3 times more frequent in women. In the case of CM, the prevalence is 2.4%[1]. According to the Study of the Global Burden of Diseases 2016[2], migraine is the sixth most prevalent disease, and its consequences imply a considerable impact both at individual and society level. Therefore, it represents an important health problem that significantly affects the quality of life, and entails both direct costs in health care and indirect costs, derived from the loss of labour productivity[3].

Migraine is caused by activation of the brain stem and the trigeminal vascular system. Upon activation, terminations of this system dilate cranial vessels that are sensitive to pain, and release algogenic neuropeptides, principally calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide, which induce dilation and inflammation. Both vascular phenomena are responsible for migraine pain[1]. The symptomatic treatment of migraine is based on the use of nonspecific drugs (nonsteroidal anti-inflammatory drugs and analgesics), specific (tryptans and ergotic derivatives) and adjuvants ones (antiemetics and prokinetics). Regarding preventive treatment, guidelines recommend the use of beta blockers (metoprolol, propranolol), antiepileptics (valproic acid, topiramate), antidepressants (amitriptyline) or calcium antagonists (flunarizine) as a first line[4]. In case of CM, if there is no response to these treatments or whether they are contraindicated, the use of botulinum toxin is recommended[3].

New monoclonal antibodies against the CGRP pathway (anti-CGRP) have recently been developed for the prevention of EM and CM, either by binding to CGRP ligand (fremanezumab, galcanezumab, eptinezumab) or receptor (erenumab)[5-7]. There are randomized clinical trials (RCTs) that evaluate these drugs[8-14]. However, the comparative efficacy among different anti-CGRP antibodies has not been elucidated. The lack of direct comparisons has hindered the selection and positioning of these new therapeutic alternatives in CM. Taking into account the social and economic impact of CM, it is essential to develop studies that provide answers to this lack of information.

The aim of this study was twofold: to develop an adjusted indirect treatment comparison (ITC) among anti-CGRP drugs in CM in terms of efficacy, using a common comparator; and to establish whether they can be considered equivalent therapeutic alternatives (ETA) in this pathology through a previously established methodology[15].

Methods

Literature search and inclusion criteria

A bibliographic search of phase II or III RCTs of anti-CGRP drugs in CM was conducted in PubMed database on December 26, 2019. The filters "clinical queries" and "narrow" were applied, and the following descriptive words were used for the search: "erenumab", "fremanezumab", "galcanezumab", "eptinezumab" and "migraine".

RCTs with similar populations, CM definition (headache of any duration or severity in 15 or more days per month, of which at least 8 days are migraine days, for at least 3 months) and same follow-up time were included. The percentage of patients with reduction of at least 50% of migraine days per month was selected as efficacy endpoint. A migraine day was defined as one in which a headache of more than four consecutive hours of duration occurs.

Data analysis

An adjusted ITC among anti-CGRP drugs was developed using Bucher's method and the Canadian Agency for Health Technology Assessment calculator[16,17]. To analyse relative efficacy, the results were compared with the drug yielding the best numerical result in the reduction of at least 50% of migraine days per month.

The ETA guide[15], which includes guidelines for positioning, was followed to establish the possible therapeutic equivalence of compared anti-CGRP drugs. This guide has already been employed for drug evaluation by the Hospital Pharmacotherapeutics Guide of Andalusia. According to ETA guide, it is necessary to establish a delta value (Δ), defined as maximum difference considered clinically irrelevant between the assessed alternatives. There is an absence of Δ reference values recognized by evaluating agencies, proposed by panels of experts, or used in RCTs of equivalence, not inferiority or sample size calculation for this endpoint. Therefore, Δ value was calculated. For this purpose, an own meta-analysis of the studies was developed, using Primo's calculator[18]. The half of the absolute risk reduction (ARR) obtained in the meta-analysis of anti-CGRP drugs vs. placebo was taken as Δ value. Heterogeneity and consistency were analysed using the Q statistic[19]. Parameter I^2 was used to determine the proportion of results variability that are due to heterogeneity and not to randomness[20]. In addition, the results were evaluated graphically to compare if ARR and its corresponding 95% Confidence Interval (95% CI) obtained in the ITC were within ± Δ margins.

To assess the potential therapeutic equivalence, safety is also necessary to be considered. To evaluate safety, the differences among adverse events (AEs) of anti-CGRP drugs were analysed.

Results

Literature search

A total of 50 studies were found. From those, 20 were excluded as they were not RCTs. The remaining 30 trials included anti-CGRP drugs

with indication in migraine: 12 RCTs of erenumab, 7 of fremanezumab, 10 of galcanezumab and 1 of eptinezumab. After discarding those RCTs that did not complied all the inclusion criteria, three of them were finally selected to develope the ITC: one of erenumab[8], one of fremanezumab[9], and another of eptinezumab[13]. The screening process was presented in figure 1.

The selected erenumab trial was a placebo-controlled phase II study with double-blinding. Patients aged between 18 and 65 years old who presented CM were included (N = 667)[8]. Patients in this CT should have presented a response to previous treatment. They were randomized in a 3:2:2 ratio to receive subcutaneous placebo, erenumab 70 mg every 4 weeks or erenumab 140 mg every 4 weeks, respectively.

The fremanezumab trial was a placebo-controlled phase III study with double-blinding[9]. Patients included (N = 1,130) had the following characteristics: age between 18 and 70 years old, diagnosed of CM and responders to the previous treatment. They were assigned in a 1:1:1 ratio to receive subcutaneous placebo, quarterly fremanezumab (625 mg at baseline and placebo at weeks 4 and 8) or monthly fremanezumab (625 mg at baseline and 225 mg at weeks 4 and 8), respectively.

The eptinezumab trial was a placebo-controlled and double-blind phase IIb study[13]. Patients aged 18-55 years and diagnosed of CM were included (N = 616). They were randomized in a 1:1:1:1:1 ratio to receive a single intravenous infusion of eptinezumab 300 mg, 100 mg, 30 mg, 10 mg or placebo.

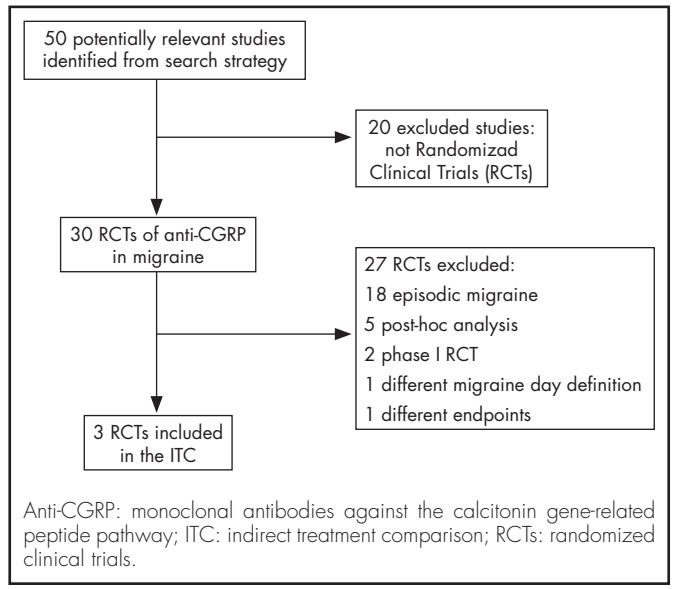
The three studies included a population of similar characteristics and defined the concept of CM in the same way: headache of any duration or severity in ≥ 15 days per month of which ≥ 8 days were migraine days. A migraine day was defined as one in which a headache of more than 4 consecutive hours of duration occurs. Eptinezumab trial also considered a migraine day as one with a headache that lasted 30 minutes to 4 hours, and believed by the patient to be a migraine that was relieved by medication. All studies presented placebo as common comparator. In these studies, the reduction of at least 50% migraine days per month was used as an efficacy endpoint, measured from the beginning until week 12.

Data analysis

The three anti-CGRP drugs evaluated, with their different dosage regimens, demonstrated superiority over placebo for the analysed endpoint in their respectives RCTs[8,9,13]. From these results, the ARR (95% IC) of each arm with active drug versus placebo was calculated. Only the ARR of eptinezumab 10 mg compared with placebo was not statistically significative. The efficacy results of RTCs and calculated ARR (95% IC) are shown in table 1. The value obtained in meta-analysis for the combined risk difference was 19% (95% CI 16-22), and the corresponding Δ, 9.5%. I^2 value was 0, and p of heterogeneity was 0.837.

Posteriorly the adjusted ITC was performed. Eptinezumab 10 mg arm was excluded from the ITC as its result was not statistically significative. Monthly fremanezumab was selected as reference treatment, as it has the best result in its RCT compared with placebo. ITC results are reflected in table 1.

Figure 1. *Flow diagram of study selection for the indirect treatment comparison.*



Anti-CGRP: monoclonal antibodies against the calcitonin gene-related peptide pathway; ITC: indirect treatment comparison; RCTs: randomized clinical trials.

Table 1. Efficacy results of each arm from selected randomized clinical trials for the analysed endpoint, and results of the indirect treatment comparison of the different alternatives vs. monthly fremanezumab based on Bucher´s method

RCT	Arms of RCT	*N*	Reduction ≥ 50% migraine days/month (response rate)	ARR vs placebo (95% CI)	Proportion of patients with reduction ≥ 50% migraine days/month ARR indirect (95% CI)
Fremanezumab	Quarterly	376	38%	20.0% (13.7 to 26.3)	–3.0% (–11.9 to 5.9)
	Monthly	379	41%	23.0% (16.7 to 29.3)	reference
	Placebo	375	18%	–	–
Erenumab	70 mg	188	40%	17.0% (8.5 to 25.6)	–6.0% (–16.6 to 4.6)
	140 mg	187	41%	18.0% (9.4 to 26.6)	–5.0% (–15.7 to 5.7)
	Placebo	281	23%	–	–
Eptinezumab	300 mg	114	57%	16.5% (3.8 to 29.2)	–6.5% (–20.7 to 7.7)
	100 mg	118	55%	14.6% (1.9 to 27.3)	–8.4% (–22.5 to 5.7)
	30 mg	117	56%	15.1% (2.4 to 27.8)	–7.9% (–22.1 to 6.3)
	10 mg	123	44%	3.4% (–9.1 to 15.9)	–
	Placebo	116	41%	–	–

ARR: absolute risk reduction; CI: confidence interval; N: number of patients; RCT: randomized clinical trials.

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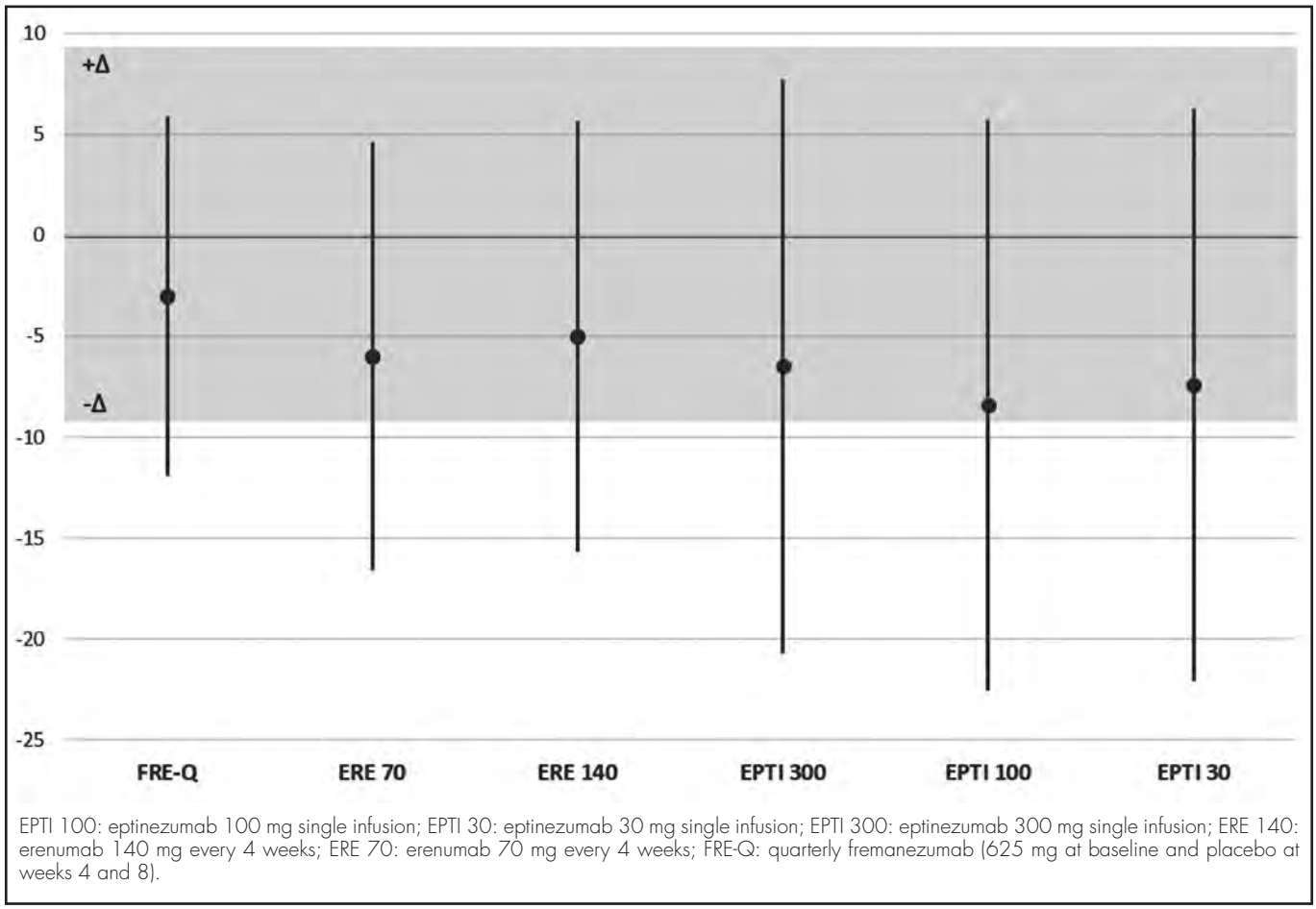
Figure 2. *Graphic results of the indirect treatment comparison: proportion of patients with reduction of ≥ 50% migraine days/month absolute risk reduction (95% CI) of different alternatives vs. monthly fremanezumab.*



EPTI 100: eptinezumab 100 mg single infusion; EPTI 30: eptinezumab 30 mg single infusion; EPTI 300: eptinezumab 300 mg single infusion; ERE 140: erenumab 140 mg every 4 weeks; ERE 70: erenumab 70 mg every 4 weeks; FRE-Q: quarterly fremanezumab (625 mg at baseline and placebo at weeks 4 and 8).

Figure 2 represents graphically the result of adjusted ITC. No statistically significant or clinically relevant differences were found between the different regimens. Moreover, most of the 95% CI is within ± Δ margins. According to the ETA guide[15], the efficacy endpoint analysed is considered as reversible because therapeutic failure does not imply serious or irreversible damage to the patients.

To evaluate safety, it was not possible to develope an ITC, due to discrepancies in the data proportioned in RCTs. The percentage of any adverse events (AEs) obtained in placebo arm were different for the three drugs: 47% in erenumab RCT, 64% in fremanezumab RCT and 56% in eptinezumab one. This fact means that the endpoint could have been measured in a different way in each RCT. Otherwise placebo results for serious AEs and AEs leading to discontinuation were similar, therefore the main differences among these two endpoints were analysed. The safety results of RTCs are shown in table 2.

All drug regimens presented a reduced proportion of serious AEs or AEs leading to discontinuation, with no significative differences from placebo. No relevant differences among the three drugs were found for these safety endpoints.

In all the analysed RCTs, the most frequent AEs were upper respiratory tract infection, nausea and nasopharyngitis, without significative differences with placebo. Injection-site pain was only recordered in erenumab and fremanezumab RCTs, due to their subcutaneus administration, but the differences were not statistically significant from placebo.

According to the obtained results in efficacy and safety, the following regimens could be considered as ETA in CM: erenumab 70 mg, erenumab 140 mg, quarterly fremanezumab, monthly fremanezumab, eptinezumab 300 mg, eptinezumab 100 mg and eptinezumab 30 mg.

Table 2. Safety results of each arm from selected randomized clinical trials for the analysed endpoints

RCT	Arms of RCT	*N*	Serious AEs *n* (%)	AEs leading to discontinuation *n* (%)
Fremanezumab	Quarterly	376	3 (< 1.0)	5 (1.0)
	Monthly	379	5 (1.0)	7 (2.0)
	Placebo	375	6 (2.0)	8 (2.0)
Erenumab	70 mg	188	6 (3.0)	0
	140 mg	187	2 (1.0)	2 (1.0)
	Placebo	281	7 (2.0)	2 (< 1.0)
Eptinezumab	300 mg	114	7 (5.8)	4 (3.3)
	100 mg	118	4 (3.3)	2 (1.6)
	30 mg	117	0	4 (3.3)
	10 mg	123	1 (0.8)	0
	Placebo	116	1 (0.8)	0

AEs: adverse events; N: number of patients; RCT: randomized clinical trials.

Discussion

The emergence of antibodies directed against the CGRP pathway could mean an additional therapeutic option in the treatment of CM. In the absence of RCTs comparing the different anti-CGRP drugs with each other, ITC and network meta-analyses are presented as interesting tools to solve this lack of clinical evidence, and to establish a position respect to the effectiveness of these drugs. In our study we can see how three of these therapeutic alternatives, erenumab, fremanezumab, and eptinezumab, probably do not show efficacy differences between them. For this, we apply the criteria established in the ETA guide[15]. We consider that a Δ value of 9.5% is acceptable as a clinical criterion of non-inferiority in the absence of an established consensus regarding the magnitude of Δ value, and taking into account that the consequences of therapeutic failure are not irreversible. In the worst case, a drug whose ARR and 95% CI remain within this range will retain at least half of the treatment effect. This therapeutic positioning promotes price competition between the three drugs, improving efficiency through lower acquisition prices[21]. Cost minimization is a strategy of great importance for the sustainability of health systems.

Our work is more conservative than other recently published studies[22-24]. Although meta-analyses are a highly valuable tool in drugs selection, their results should only be considered when studies with similar populations or drug patterns are included. The interpretation of results from studies that include heterogeneous populations[22-24] inherently involves a high degree of uncertainty that could have significant clinical or pharmacoeconomic implications. A frequent mistake of CM meta-analyses published to date is the inclusion of RCTs with different definitions of migraine, or refractory populations and non-refractory to previous treatment lines. The selection of studies with a population diagnosed of EM[10-12] or with different consideration of a migraine day duration, as galcanezumab trial in CM does[14], entails a considerable bias. Our work only compares those RCTs that could be comparable according to populations included, intervention arm, comparator and assessed endpoint. The main limitation of comparisons between anti-CGRP drugs is the lack of data that allow reliable comparisons to be established between all antibodies acting on CM.

A limitation of our study is that ITC was performed among three studies of different design. While the results of erenumab and eptinezumab belong to a phase II RCT[8,13], the fremanezumab data were extracted from a phase III RCT[9]. Taking into account the characteristics of RCTs, phase II results are usually immature and should be considered with caution, and phase III RCTs present more conclusive data. However, the lack of similar studies makes it impossible to develop any other comparison among RCTs of identical design. Moreover, the eptinezumab trial included patients with migraine days duration of both more than 4 hours and between 30 minutes and 4 hours. This fact could entail a bias that affects the results, since this trial could be including a part of the population with more attenuated migraine characteristics than in the other two studies.

The recent marketing authorisation of anti-CGRP drugs against CM and its possible economic impact, as well as the important socio-economic repercussions of the pathology, make it necessary to perform studies such as this one for the therapeutic positioning of available therapeutic alternatives.

In conclusion, our ITC showed no differences in the reduction of at least 50% of monthly migraine days between erenumab, fremanezumab and eptinezumab in different pharmacological regimens, and no significative differences in safety were found among the three drugs. Thus, with the currently available scientific evidence, these drugs could be considered ETA in CM.

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Conflict of interests

No conflict of interest.

Contribution to the scientific literature

This is the first adjusted indirect comparison among anti-CGRP drugs in chronic migraine that includes those trials that could be comparable according to populations, disease definition and assessed endpoints.

The results of our work allow to establish whether these drugs could be considered as equivalent therapeutic alternatives in this patology.

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