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

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 gene-related 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 gene-related 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

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.
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 aj Compound (n = 1). Three studies were selected: one of erenumab, one of fremanezumab and another of galcanezumab. 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 galcanezumab. 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.

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 neurologic symptoms (visual or sensorial) called aura. 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%. According to the Study of the Global Burden of Diseases 2016, 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.

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. The symptomatic treatment of migraine is based on the use of nonspecific drugs (nonsteroidal anti-inflammatory drugs and analgesics), specific (triptans and ergot derivatives) and adjuvant 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. In case of CM, if there is no response to these treatments or whether they are contraindicated, the use of botulinum toxin is recommended.

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). There are randomized clinical trials (RCTs) that evaluate these drugs. 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.

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 Buecher’s method and the Canadian Agency for Health Technology Assessment calculator (1-3). 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 (4), 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 metraanalysis of the studies was developed, using Primo’s calculator (5). The half of the absolute risk reduction (ARR) obtained in the metaanalysis of anti-CGRP drugs vs. placebo was taken as Δ value. Heterogeneity and consistency were analysed using the Q statistic (6). Parameter I² was used to determine the proportion of results variability that are due to heterogeneity and not to randomness. 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 30 remaining 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 comply all the inclusion criteria, three of them were finally selected to develop the ITC: one of erenumab, one of fremanezumab, and another of eptinezumab. 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 \( (N = 667) \). 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. 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. 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 respective RCTs\(^8\),\(^9\),\(^13\). From these results, the ARR (95% CI) 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 RCTs and calculated ARR (95% CI) are shown in table 1. The value obtained in metanalysis for the combined risk difference was 19% (95% CI 16-22), and the corresponding Δ, 9.5%. I² 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.

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

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

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

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

50 potentially relevant studies identified from search strategy

20 excluded studies: not Randomized Clinical Trials (RCTs)

30 RCTs of anti-CGRP in migraine

27 RCTs excluded:
18 episodic migraine
5 posthoc analysis
2 phase I RCT
1 different migraine day definition
1 different endpoints

Anti-CGRP: monoclonal antibodies against the calcitonin gene-related peptide pathway; ITC: indirect treatment comparison; RCT: randomized clinical trials.
Monoclonal antibodies against calcitonin gene-related peptide in chronic migraine: an adjusted indirect treatment comparison

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.

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

<table>
<thead>
<tr>
<th>RCT</th>
<th>Arms of RCT</th>
<th>N</th>
<th>Serious AEs n(%)</th>
<th>AEs leading to discontinuation n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fremanezumab</td>
<td>Quarterly</td>
<td>376</td>
<td>3 (&lt; 1.0)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td></td>
<td>Monthly</td>
<td>379</td>
<td>5 (1.0)</td>
<td>7 (2.0)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>375</td>
<td>6 (2.0)</td>
<td>8 (2.0)</td>
</tr>
<tr>
<td></td>
<td>70 mg</td>
<td>188</td>
<td>6 (3.0)</td>
<td>0</td>
</tr>
<tr>
<td>Erenumab</td>
<td>140 mg</td>
<td>187</td>
<td>2 (1.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>281</td>
<td>7 (2.0)</td>
<td>2 (&lt; 1.0)</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td>114</td>
<td>7 (5.8)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
<td>118</td>
<td>4 (3.3)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Epitinezumab</td>
<td>30 mg</td>
<td>117</td>
<td>0</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>123</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>116</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

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 regarding 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. 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 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. Cost minimization is a strategy of great importance for the sustainability of health systems.

Our work is more conservative than other recently published studies. Although meta-analyses are a highly valuable tool in drug 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 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 or with different consideration of a migraine day duration, as galcanezumab trial in CM does, 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, the fremanezumab data were extracted from a phase III RCT. 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 significant differences in safety were found among the three drugs. Thus, with the currently available scientific evidence, these drugs could be considered ETA in CM.

Funding

No funding.

Acknowledgements

The authors wish to thank Emilio Jesús Alegre del Rey, from the Pharmacy Department of the Puerto Real University Hospital, for his assistance in preparing the final draft of this manuscript.

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 pathology.

Bibliography

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


17. Wells GA, Sultan SA, Chen L, Khan M-GD. Indirect Evidence: Indirect Treatment Comparisons in Meta-Analysis [Internet monograph]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009 [accessed 12/23/2019]. Available at: https://www.researchgate.net/profile/Shagufta_Sultan/publication/26411972_Canadian_Agency_for_Drugs_and_Technologies_in_Health_Indirect_Evidence_Indirect_Treatment_Comparisons_in_Meta-Analysis_Publications_can_be_requested_from_Canadian_Agency_for_Drugs_and_Technologies_in.pdf


