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Artículos originales

Práctica clínica en prevención de migraña con anticuerpos monoclonales del péptido relacionado con el gen calcitonina: evidencias de casos reales

Clinical practice in prevention of migraine with calcitonin-gene related peptide monoclonal antibodies: real-world evidence

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Resumen

Introducción: Los anticuerpos monoclonales (mAbs) del péptido relacionado con el gen de la calcitonina (CGRP) son un novedoso tratamiento para prevenir la migraña crónica y la episódica de alta frecuencia.

Método: Se realizó un estudio observacional, retrospectivo, multicéntrico para analizar la efectividad y seguridad de los mAbs anti-CGRP (erenumab, galcanezumab, fremanezumab). La variable de efectividad fue la reducción en los días de migraña al mes (MMDs). La seguridad se midió con los efectos adversos descritos.

Resultados: Los resultados de 127 pacientes muestran efectividad similar entre erenumab y galcanezumab en la reducción de los MMDs. Una proporción importante de pacientes cambió de mAb por pérdida de respuesta o fallo primario tras una media de 7 meses: 15,11% erenumab; 24% galcanezumab. Algunos pacientes se trataron concomitantemente con toxina botulínica A: 8,13% erenumab; 12% galcanezumab; 6,25% fremanezumab. Más del 60% de pacientes habían sido tratados previamente con toxina botulínica A con falta de respuesta tras varias dosis. Se describieron efectos adversos cardiovasculares (dolor en el pecho, taquicardia) exclusivamente en pacientes con erenumab.

Conclusiones: La práctica clínica actual se basa en el intercambio de mABs anti-CGRP en casos de falta de respuesta o migraña refractaria, aunque su evidencia es limitada y se ha demostrado que la efectividad entre los tres fármacos es equivalente. Las Agencias Reguladoras recomiendan un período de 12 semanas para evaluar la efectividad del mAb. La mitad de los pacientes refirieron falta de seguimiento por Neurología. Los farmacéuticos clínicos son necesarios en la atención integrada de la migraña.

Palabras clave: Migraña; péptido relacionado con el gen calcitonina; antagonistas del receptor del péptido relacionado con el gen de la calcitonina.

Abstract

Introduction: Calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) are novel therapeutic option for prevention of chronic migraine (CM) and high-frequency episodic migraine (HFEM).

Method: An observational, retrospective, multicentre, real-world evidence study was developed to analyse the effectiveness and safety of anti-CGRP mAbs (erenumab, galcanezumab, fremanezumab). Effectiveness was measured by monthly migraine days (MMDs) reduction. Adverse events were recorded for safety outcome.

Results: Results from 127 patients showed similar effectiveness between erenumab and galcanezumab in MMDs reduction. A notable proportion of patients switched of mAb because of loss of response or primary no-response after seven months: 15.11% erenumab; 24% galcanezumab. Some patients were concomitant treated with Onabotulinumtoxin A (Onabot A): 8.13% erenumab; 12% galcanezumab; 6.25% fremanezumab. More than 60% of the total were previously treated with Onabot A with loss of response. Cardiovascular adverse events are exclusively reported by erenumab group (chest pain, tachycardia).

Conclusions: Current clinical practice is based on switching of CGRP mAbs after loss of response or refractory migraine, even though evidence for this practice is limited and effectiveness between the drugs has been demonstrated to be equivalent. The period of 12 weeks since the first dose of the CGRP mAb, recommended by Regulatory Agencies, should be respected to determine if the mAb selected is being ineffective. At least, half of the patients complained about lack of follow-up by reference neurologist. Clinical pharmacists are important to help these patients manage the burden of migraine.

Keywords: Migraine; calcitonin gene-related peptide; calcitonin gene-related peptide receptor antagonists

Highlights

The new anti-CGRP monoclonal antibodies are effective in reducing migraine days per month in an equivalent way among them.

Current clinical practice is based on switching between mAbs in patients with refractory migraine, as well as the concomitant use of botulinum toxin A. However, the evidence for these practices is limited.

This study provides the real-world experience of efficacy and safety in migraine prevention with anti-CGRP mAbs. The results show that switching between mAbs is ineffective in reducing MMDS in refractory migraines.

Introduction

Migraine is a chronic neurological disorder consisting of recurring headache of moderate to severe intensity lasting 4-72 hours. The headache is usually unilateral, pulsatile, the pain is often worse with physical activity and is associated with sensibility to light and sound and/or nausea. People who experience frequent attacks of migraine can have either episodic or chronic migraine (CM)[1,2].

High frequency episodic migraines (HFEM) are defined as headaches occurring less than 15 days per month. CM is defined as headache occurring on 15 or more days per month for more than 3 months[1].

Chronic migraine is usually associated with greater disability and prevalence of comorbidities such as anxiety, depression and other chronic disorders[3]. This can greatly affect the quality of daily life, generating an important charge for the family and society. Therefore, a treatment approach that considers different therapeutic targets taking into account the pathophysiology of migraine could improve outcomes[4].

Results from the International Burden of Migraine Study (IBMS)[5] show that Spain was the country with the highest per patient annual cost in both CM and HFEM compared to other four of the European Union (Italy, Germany, France, UK).

Traditional treatments are not specific for migraine but include antiepileptic drugs, β-blockers and antidepressants[1,6]. These treatments have failed to reduce the economic and social burden of migraine, considered the main cause of neurological disability and one of the main causes of long-term disability. Also, the success of these older drugs has been limited by poor adherence by the patient, low efficacy and tolerability[7].

Since 2010, OnabotulinumtoxinA (Onabot A) is approved for the prevention of chronic migraine. Onabot A reduces the magnitude of pain signalling in the brain and prevents activation and sensitization of central neurons thought to be involved in migraine chronification[3]. Thus, it attenuates the release of neuropeptides and neurotransmitters such as glutamate, substance P, and calcitonin gene–related peptide (CGRP)[3,8].

Recently, direct inhibition of CGRP pathways has emerged as a targeted approach for migraine prevention. In 2018, the FDA approved three drugs, administered subcutaneously, for the preventive treatment of migraine in adults: erenumab, galcanezumab and fremanezumab[9]. These drugs are monoclonal antibodies (mAbs) antagonists of the CGRP that are able to relieve an acute headache attack, with or without aura. The mechanism of action differs between them, erenumab acts by binding to the CGRP receptor, competes with the peptide and inhibits its function at the receptor, whereas fremanezumab and galcanezumab selectively bind to the CGRP ligand and block its binding to the receptor. Adverse effects (AEs) reported include constipation, rhinitis and cardiovascular adverse reactions that should be taken into account during follow-up of patients[10].

Risks of long-term CGRP blockade

Currently, the risks of long-term blocking of CGRP signalling are not known. The CGRP peptide acts throughout the body, therefore, circulating antibodies could affect all peripherally accessible sites where CGRP acts[1,11].

One concern is the chronic reduction of CGRP in the vascular system, where it acts as a potent vasodilator. This could cause cardiovascular disorders such as hypertension, cardiac dysfunction and episodes of coronary or cerebral ischaemia[11]. Therefore, as with any new class of drug, continued monitoring of various patient populations for risks associated with long-term treatment of CGRP-related antibodies is important[1].

Thus, the aim of this study is to analyse the effectiveness and safety of anti-CGRP mAbs in patients with either CM or HFEM. As well, our purpose is to analyse the effectiveness of switching between mAbs in refractory patients, as well as the concomitant use of Onabot A, which are emerging as new current clinical practice.

Methods

This observational, retrospective, multicentre study was carried out between March 2019 and April 2021 at one third level and one first level hospital. The inclusion criteria were patients treated with a CGRP monoclonal antibody (mAb) therapy (erenumab, galcanezumab or fremanezumab) for at least 3 months diagnosed of CM or HFEM. Patients in treatment with these drugs accepted to collect demographic and clinical data, confidentially, related to efficacy and safety of their treatment during pharmacy visits.

Baseline demographic and clinical characteristics were recorded from electronic medical records and prescription records. When mAb therapy is prescribed for the first time, pharmacists record patient's basal characteristic such as type of migraine diagnosed and monthly migraine days (MMDs) before initiating mAb treatment. During the next pharmacy visits, the pharmacist records any relevant adverse effect related to treatment and reasons to discontinuation. At 3, 6 and 12-month period with active treatment, monthly migraine days are recorded again (per-patient self-reported).

Clinical and safety data included: treatment received (type of CGRP mAb and dose), changes in dose or treatment during follow-up period, number of doses received until change of mAb or dose increase), total number of doses received, previous mAb treatment (yes/no), monthly migraine days (MMDs) at baseline and at 3, 6 or 12-month period (if applicable), previous treatment with Onabot A (yes/no), concomitant treatment with Onabot A (yes/no), other concomitant treatment (drug therapy group), cardiovascular adverse effects (AEs) related to mAb and other AEs.

In order to analyse the effect in change of MMDs from baseline to 3, 6 or 12 months after mAb treatment, we performed a paired Student t-test. The statistical analysis was performed with program R® version 3.6.2. We applied the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement in the conduct of this study.

Results

A total of 127 patients met the inclusion criteria: 86 patients treated with erenumab, 25 with galcanezumab and 16 with fremanezumab for at least 3 months. Demographic and clinical characteristics are summarized in Table 1 stratified by treatment. Independently of the mAb, most patients were female (>75%) and most patients were diagnosed of CM.

Related to patients treated with erenumab, the mean age was 47 years (range, 17-69). All patients were adults except one patient with 17 years. Clinicians prescribed the lowest dose (erenumab 70 mg) at initial of treatment with CGRP mAb to 94.2 % (81/86) of patients and 55.8% (48/86) required a dose increase because of inadequate or loss of response. The mean number of doses administered until dose increase or change to other CGRP mAb was 4.4 (3-6) and the mean number of total doses administered was 8 (6-11). The 11.62% (10/86) of patients changed to a second CGRP mAb and 3.5% (3/86) changed to a third CGRP mAb, either of loss of response or adverse effects such as constipation. The median MMDs at baseline was 11.8 (9-15) and 5.1 (2-7) after 3, 6 or 12 months. We performed a paired t-Student test to evaluate this outcome and the results were statistically significant ($p < 0.01$).

The subjective perception of lower intensity of migraines was reported by 96.5% (83/86) of patients. At baseline, 83.7 % of patients had been treated with Onabot A and during the period with erenumab, 8.13 % (72/86) received concomitant treatment with Onabot A. Other drugs used were triptans (43 %), non-steroidal anti-inflammatory drugs (NSAIDs) (9.3, opioids (3.5 %), antidepressants (12.7 %), antiepileptics (8.14 %) During pharmacy visits, 3.5 % (3/86) of patients treated with erenumab reported cardiovascular (CV) adverse events: 2 patients referred chest pain and 1 patient tachycardia. Most common non-cardiovascular adverse effect reported was constipation (9.3%), intense itching (3.5%), malaise (3.5 %), insomnia (2.3 %), rhinitis (2.3 %) and headache worsening (2.3 %). More than 20% (20/86) of patients reported any of these non-CV adverse event.

Demographic results for patients treated with galcanezumab are similar with mean age of 45 years (range, 22-67) and 76 % (19/25) female patients. Only 3 patients (12%) had HFEM disease. Almost half of the patients (44%) were previously treated with other CGRP mAb (erenumab) and 6 of 25 patients needed to change to other CGRP mAb because of loss of response or intolerance. The mean number of doses administered until change of molecule was 7,5 [3,5-9,5]. The median number of MMDs at baseline was 12 (8-15) and 5 (3-6,25) after 3,6 or 12 months. Paired t-test showed statistically significant results for the difference in MMDs (p=6,8e-5). However, if we analyse in detail the results from patients previously treated with erenumab, the mean of MMDs only differs slightly from 12 days when they were treated with erenumab to 8 days after galcanezumab.

Subjective improvement in intensity of migraines was reported by 76% (19/25) of patients. Three patients (12%) had concomitant treatment with Onabot A. Other drugs prescribed were triptans (40%), antiepileptics (20%), antidepressants (16%), NSAIDs (4%) and opioids (4%). None of the patients reported any CV adverse effect, but some patients complained about end-of-dose effect (12%), constipation (4%) and headache worsening (4%).

Data for fremanezumab group is limited because of the small proportion of patients meeting the inclusion criteria. Safety and effectiveness results are not described for fremanezumab because records at pharmacy visits had not been obtained yet. Mean age is 51.8 years (range 34-71) and 81.25% (13/16) are female patients. Two patients included are diagnosed of HFEM (12.5%). Half of the cohort had been previously treated with any CGRP mAb and 100% (16/16) of the patients initiated with the lowest dose of fremanezumab (225 mg) and, until date, no one has required dose increment. Median MMDs has just been measured at baseline: 11.8 [10-14.25]. Nearly 100% (15/16) of patients were previously treated with Onabot A and 6.25% (1/16) received Onabot A combined with mAb. Other preventive and acute-treatments prescribed were triptans (50%), NSAIDs (18.75%) and opioids (12.5%). At pharmacy visits, at least half of the patients complained about lack of follow-up by reference neurologist independently of the mAb prescribed.

Table 1. Principal patients' characteristics, clinical and safety data of erenumab, galcanezumab and fremanezumab.

CHARACTERISTICS	ERENUMAB (n= 86)	GALCANEZUMAB (n= 25)	FREMANEZUMAB (n= 16)
Age, years (mean)	47 (17-69)	45 (22-67)	51.8 (34-71)
Sex (n, %) Female Male	68 (79 %) 18 (21 %)	19 (76 %) 6 (14 %)	 13 (81.25 %) 3 (18.75 %)
Diagnostic, type of migraine Chronic migraine High frequency episodic disease	61 (70.9 %) 25 (29.1 %)	22 (88 %) 3 (12 %)	14 (87.5 %) 2 (12.5 %)
Previous CGRP mAb	No	11 (44%, erenumab)	8 (50 %)
Lowest dose at initial of treatment (n, %)	81 (94.2 %)	NA	16 (100 %)
Need of dose increase	48 (55.8 %)	NA	No

CHARACTERISTICS	ERENUMAB (n= 86)	GALCANEZUMAB (n= 25)	FREMANEZUMAB (n= 16)
Need of change to another mAb (n, %)	13 (15.11 %)	6 (24 %)	No
-Change to a second mAb (n, %)	10 (11.62 %)	6 (24 %)	
-Change to a third mAb (n, %)	3 (3.5 %)	NA	
Mean nº of doses administered until dose increase or change in treatment (IC 95%)	4.4 [3-6]	7.5 [3.5-9.5]	NA
Mean total nº of doses administered (IC 95%)	8 [6-11]	7.7 [5-10]	3.7 [3-4]
Mean nº of MMDs at baseline (IC 95%)	11.8 [9-15]	12 [8-15]	11.8 [10-14,25]
Mean nº of MMDs after mAb (3, 6 or 12 months)	5.1 [2-7]	5 [3-6.25]	-
Subjective improvement in intensity of migraines (yes/no)	83 (96.5 %)	19 (76 %)	-
Previous treatment with Onabot A (n %)	72 (83.7 %)	16 (64 %)	15 (93.75 %)
Concomitant treatment with Onabot A (n %)	7 (8.13 %)	3 (12 %)	1 (6.25 %)
Other concomitant treatment: -Triptans -NSAIDs -Opioids -Antidepressants -Anti-epileptics	 37 (43 %) 8 (9.3 %) 3 (3.5 %) 11 (12.7 %) 7 (8.14 %)	 10 (40 %) 1 (4 %) 1 (4 %) 4 (16 %) 5 (20 %)	 8 (50 %) 3 (18.75 %) 2 (12.5 %) NA NA
CV AEs (n, %) -Chest pain -Tachycardia	3 (3.5 %) 2 (2.3 %) 1 (1.16 %)	No	-
Other AEs (n, %)	20 (23.25 %)	5 (20 %)	-
-Constipation	8 (9.3 %)	1 (4 %)	
-End-of-dose effect	NA	3 (12 %)	
-Intense itching	3 (3.5 %)	NA	
-Malaise	3 (3.5 %)	NA	
-Insomnia	2 (2.3 %)	NA	
-Rhinitis	2 (2.3 %)	NA	
-Headache worsening	2 (2.3 %)	1 (4 %)	

CGRP mAb: monoclonal antibody anti-calcitonin gene-related peptide; MMDs: monthly migraine days; NSAIDs: Non-steroidal anti-inflammatory drugs; CV: cardiovascular; AEs: adverse effects; NA: Not applicable; -: Data not available

Discussion

In the present real-life experience, we observed a significant and similar reduction in the number of MMDs across the groups of erenumab and galcanezumab with similar results, as well, in subjective improvement in intensity of migraines reported by patients. It has been demonstrated that CGRP mAbs are a new effective preventive treatment of migraines for a huge proportion of patients that, also, indirectly, improve patients' life quality. But, an outstanding number of patients do not respond satisfactorily to these new molecules, as they are primary non-responders or they lose response after a few months[3,12].

As reported by our colleagues Briceño-Casado et al.[12] in a case of series, a notable proportion of patients changed to another mAb because of loss of response or primary no-response. Our results show that even a small proportion of patients switched to a third mAb because of inefficacy to the both previous mAb administered. Currently at clinical practice, the strategy for these patients which do not respond to a first CGRP mAb, is based on switching of CGRP mAbs, even though evidence for this practice is limited[12]. We observed that non-responders' patients treated with erenumab did not achieve notorious reduction y MMDs despite switching to galcanezumab. Even so, a small proportion of patients switched to fremanezumab for one last chance. Lack of evidence for switching of anti-CGRP molecules was already described in the position report of fremanezumab for the prevention of migraine by the Spanish Agency of Medicines and Medical Devices[13]. As the effectiveness of these drugs seems to be equivalent, it could be reasonable to stablish the therapeutic alternative based on efficiency criteria and cost minimization strategy[14].

In the meta-analysis performed by Briceño-Casado et al.[14], there were also no differences between CGRP mAbs in terms of safety. In our study, CV adverse events are exclusively reported by patients treated with erenumab and not by those treated with galcanezumab. Two patients reported chest pain and one patient reported tachycardia. Although these effects were not serious, the safety profile of the molecules could be another key point in the selection of the CGRP mAb.

Blumenfeld et al.[3], recently reported real-world evidence about concomitant treatment of CGRP mAbs and Onabotulinumtoxin A for those patient's refractory to monotherapy with CGRP mAbs. Results from our study demonstrate that this is, as well, a clinical practice starting to emerge as an option to enhance the effect of the mAb for highly refractory patients that have not respond to one or two mAb or do not achieve sufficient reduction in MMDs. It is important to point that more than 60% of patients either treated with erenumab, galcanezumab or fremanezumab had been previously treated with Onabotulinumtoxin A with loss of response after several doses. Combination of CGRP mAbs and Onabotulinumtoxin A is based on an additive effect preventing the activation of various pain fibers.

Follow-up of patients with CM or HFEM treated with CGRP mAbs is mandatory. Regulatory Agencies strongly recommend a minimum of 12 weeks since the first dose of the CGRP mAb to determine if the mAb selected is not being effective[13,15]. But, in clinical practice, we observed that some patients switched to other CGRP mAb in assumption of loss of response before this period of time. By the other hand, once the preventive treatment is well stablished, it is important to emphasize to the patient the importance of taking medication for acute crisis.

As well, it is essential to detect those patients that have problems with the CGRP mAb because of ineffectiveness or AEs. We observed that more than a half of patients complained at pharmacy visits of lack of follow-up by neurologist and reported problems with the medication. Follow-up by pharmacists should include patient reported outcome measures (PROMs) as the Migraine Disability Assessment test (MIDAS) or the headache impact test (HIT-6) and records of safety outcomes.

Limitations of the study

Results for the outcome number of MMDs at 3, 6 or 12 months were treated together as at the moment of cut-off some patients had been followed-up for 3 or 6 months and the rest of them for 12 months. Subgroup's analysis would have been an ideal option for the management of this outcome that could not be performed. Related to fremanezumab, there is no data for effectiveness or safety outcomes because patients had received less than 3 doses by the time of cut-off. Thus, comparisons of effectiveness and safety between the three groups were limited.

Conclusion

CGRP mAbs are similarly effective in the reduction of MMDs, but switching of mAbs in non-responders' patients might not have significant impact. Concomitant treatment of CGRP mAbs and Onabotulinumtoxin A for refractory patients is a new clinical practice that may have positive results but may be explored with caution because of limited evidence. Follow-up of patients is the best tool to ensure

the effectiveness and safety of these new molecules. Clinical pharmacists have a new field of action in the prevention and treatment of CM and HFEM to help these patients manage the burden of migraine.

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