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Review

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Anti-CGRP Monoclonal Antibodies for the Treatment of Chronic and Episodic Migraines

Anticuerpos monoclonales contra el CGRP para el tratamiento de la migraña crónica y episódica

Abstract

Migraine is a clinical condition that causes neurological disability in a high percentage of the economically active population. This disorder is characterized by pulsatile unilateral headache accompanied by other neurovascular phenomena. The disease can acquire a chronic behavior forcing patients to receive preventive treatment for a long time period. However, many drugs currently available for the chronic treatment cause different side effects that limit their use and most of them were not designed specifically for migraine prevention. Evidence of the role that calcitonin gene related peptide (CGRP) plays in the mechanisms of central sensitization and in the physiopathology of migraine has led to the development of therapies directed to limit its biological activity, among which there are four new monoclonal antibodies against that molecule or its receptor. Clinical trials carried out so far with these antibodies provide evidence in favor of their use in the treatment and control of migraine, therefore, in this review we discuss the results of such studies and provide the physiological and molecular bases that support the use of the CGRP as a therapeutic target.

Keywords

Calcitonin gene related peptide, migraine, monoclonal antibodies, headache

Resumen

La migraña es una condición clínica que provoca discapacidad en un porcentaje alto de la población económicamente activa. Este padecimiento se caracteriza por una cefalea unilateral pulsátil acompañada de otros fenómenos neurovasculares. La enfermedad puede adquirir un comportamiento crónico que obliga al paciente a recibir un tratamiento preventivo por un largo periodo de tiempo. Sin embargo, muchos fármacos hoy disponibles para dicho propósito causan diferentes efectos adversos que limitan su uso y la mayoría de ellos no fueron diseñados específicamente para la prevención de la migraña. La evidencia de la participación del péptido relacionado con el gen de la calcitonina (CGRP) en los mecanismos de sensibilización central al dolor y en la fisiopatología de la migraña ha llevado al desarrollo de tratamientos dirigidos a limitar su actividad biológica, entre los que se encuentran cuatro nuevos anticuerpos monoclonales contra dicha molécula o su receptor. Los ensayos clínicos hasta ahora realizados con estos anticuerpos aportan evidencia a favor de su empleo en el tratamiento y control de la migraña, por lo que en esta revisión se discuten los resultados de dichos estudios y se proveen las bases fisiológicas y moleculares que sustentan el uso del CGRP como blanco terapéutico.

Palabras clave

Péptido relacionado con el gen de la calcitonina, migraña, anticuerpos monoclonales, cefalea.

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Introducción

Migraine is one of the main causes of disability worldwide. It is estimated that 15% of the population under the age of 50 suffer from this neurological disorder, which has a higher prevalence in women than in men.[1] It is characterized by the presence of a pulsatile unilateral headache of moderate to severe intensity, aggravated by movement, lasting 4 to 72 hours, accompanied by nausea or vomiting, phonophobia and photophobia.[2] In most patients, headache occurs less than 15 days per month (episodic migraine); however, 2 to 3% of the subjects will develop a chronic form of the disease[3] defined as the occurrence of 15 or more days with headache per month for more than three months, with at least eight of these pain attacks fulfilling the characteristics of a migraine, with or without aura, which can decrease with a triptan or ergotamine derivative, and for which there is no other alternative diagnosis within the definitions of the latest International Classification of Headaches, 3rd edition, recently published.[2]

Chronic migraine causes a great impact on the quality of life of patients, affecting their work life and interpersonal relationships.[3,4] Recurrent pain attacks require the initiation of prophylactic treatment with any of the drugs currently available for this purpose,[5] which include anticonvulsants, tricyclic antidepressants, beta blockers, and calcium channel blockers.[6] However, adherence to treatment is affected by the high incidence of adverse effects and drug interactions of these medications, of which none was developed specifically for the management of migraine.[7,8] In fact, onabotulinum toxin A is the only drug approved by the FDA for the management of chronic migraine, although it does not dramatically reduce the number of days with headache.[9-11] Therefore, there is an urgent need for drugs aimed at counteracting the underlying pathophysiological mechanisms of chronic migraine. Evidence generated for more than 30 years supports the participation of the calcitonin gene-related peptide (CGRP) in the functional alterations that lead to the central sensitization to pain in subjects with headache, supporting its use as a new therapeutic target.[12] Recent efforts have been aimed at interrupting the activity of CGRP from different approaches, the most novel of which is the use of humanized monoclonal antibodies directed to neutralize the peptide or to block its receptor. The results of the clinical trials to date with these antibodies in patients with chronic and episodic migraine show positive results that could represent a new era in the management of this condition, although their safety and cost-benefit must be analyzed before displacing other therapeutic measures currently in use. Therefore, in this review, we provide a summary of the evidence derived from basic and clinical research that supports the use of anti-CGRP monoclonal antibodies for the preventive treatment of migraine.

Cgrp as a therapeutic target: physiopathological and molecular basis

Migraine is a disorder whose origin is still unknown. Although for a long time it was considered a vascular disorder, recent evidence suggests that there is a primary neurogenic cause with secondary vascular phenomena.[13] What is clear is the involvement of the trigeminal nerve and the nucleus caudalis in the mechanisms of initiation and maintenance of pain sensitization underlying chronic migraine,[14] probably through its activation by peripheral inflammatory mediators or by a dysfunction in the processing of afferent stimuli that could be misinterpreted as painful and accessing the central sensory areas through the trigeminovascular system.[14,15]

The CGRP is a 37-amino acid neuropeptide involved in the central and peripheral events of migraine.[16,17] It belongs to the calcitonin family along with amylin, adrenomedullin-2, and adrenomedullin.[18] It is encoded by the same calcitonin gene through an alternative splicing mechanism of mRNA, which generates two isoforms of CGRP. Both isoforms are preferentially expressed in nerve tissue, especially in A delta and C fibers; the alpha isoform is present

in the trigeminal nerve terminals and the beta isoform predominates in the enteric peripheral nervous system.[19, 20] The two peptides exert their activity through their binding to their receptor, which is heterodimeric and is composed of three subunits: calcitonin receptor-like receptor (CLR, protein with 7-transmembrane domains), receptor activity-modifying protein (RAMP1), and receptor component protein (RCP).[21] The CGRP is a potent vasodilator which made it a candidate to be an active mediator during migraine attacks.[12,16,22] Currently, due to its different functions, it is believed that its participation is crucial to increase sensory activity at different levels since it is a neuromodulator that can potentiate glutamate-mediated synaptic transmission leading to central sensitization in trigeminal sensory terminals and other central nuclei.[23-25] During spontaneous or induced migraine events, CGRP levels rise markedly and can be measured in different biological samples.[16] Likewise, administration of the recombinant peptide induces migraine attacks in subjects with the disease and headache symptoms in healthy individuals.[26,27] Treatment with triptans drastically decreases CGRP concentrations and the measurement of this molecule has been proposed as a biomarker of the disease.[28,29] However, by far the most solid evidence supporting the participation of this peptide in the pathophysiological mechanisms of migraine was provided by clinical trials conducted with CGRP receptor antagonists called gepants, of which only the ubrogepant continues to be tested in clinical trials (NCT02828020) because the rest caused concerns about potential liver toxicity.[30-35] In these studies, it was observed that the antagonism of the signaling mediated by the binding of CGRP to its receptor significantly decreased the frequency and duration of migraine attacks.

Based on clinical and molecular evidence, the current model suggests that some migraine-initiating stimuli induce an elevation of CGRP levels, increasing synaptic transmission and resulting in pain and altered sensory perception.[17] However, this peptide could also contribute to the mechanisms of neurogenic inflammation, peripheral sensitization, aversion to light, cortical depression, and vasodilation that occur in migraine.[36]

Clinical trials with monoclonal antibodies targeting cgrp or its receptor

To date, four humanized antibodies directed against CGRP have been developed with which clinical trials are being carried out. Of these four, Fremanezumab, Eptinezumab, and Galcanezumab bind specifically to the peptide, and Erenumab blocks the CGRP receptor.

A meta-analysis conducted in 2017 reported that, in general, antibodies against CGRP significantly reduce migraine days per month from baseline with an average of 1.6 days compared with the placebo group.[37] Following this meta-analysis, four more advanced clinical trials have been published, the results of which are shown in Table 1. The most important characteristics of each antibody are summarized below as well as the studies that support its use in the preventive treatment of migraine.

Fremanezumab

Fremanezumab (TEV-48125) is a humanized monoclonal antibody isotype IgG2a that binds selectively to the alpha and beta isoforms of CGRP.[38] Its low nonspecific reactivity against other molecules structurally related to CGRP diminishes its potential to induce toxicity. Pre-clinical studies demonstrated its efficacy in interfering with CGRP signaling through its receptor in vitro. The first in vivo tests in rats showed that Fremanezumab is capable of inhibiting the vasodilatation of the middle meningeal artery in response to electrical stimulation. Likewise, in non-human primates (NHP), this antibody counteracted the vasodilatory response induced by the administration of capsaicin in a dose-dependent manner.[39] Its long half-life initially caused concern about the possible impact of chronic inhibition of CGRP on cardiovascular function. However, in a study conducted in NHP, no alterations in cardiovascular parameters were observed after chronic administration for 14 weeks and, in six phase I trials, the administration of Fremanezumab intravenously

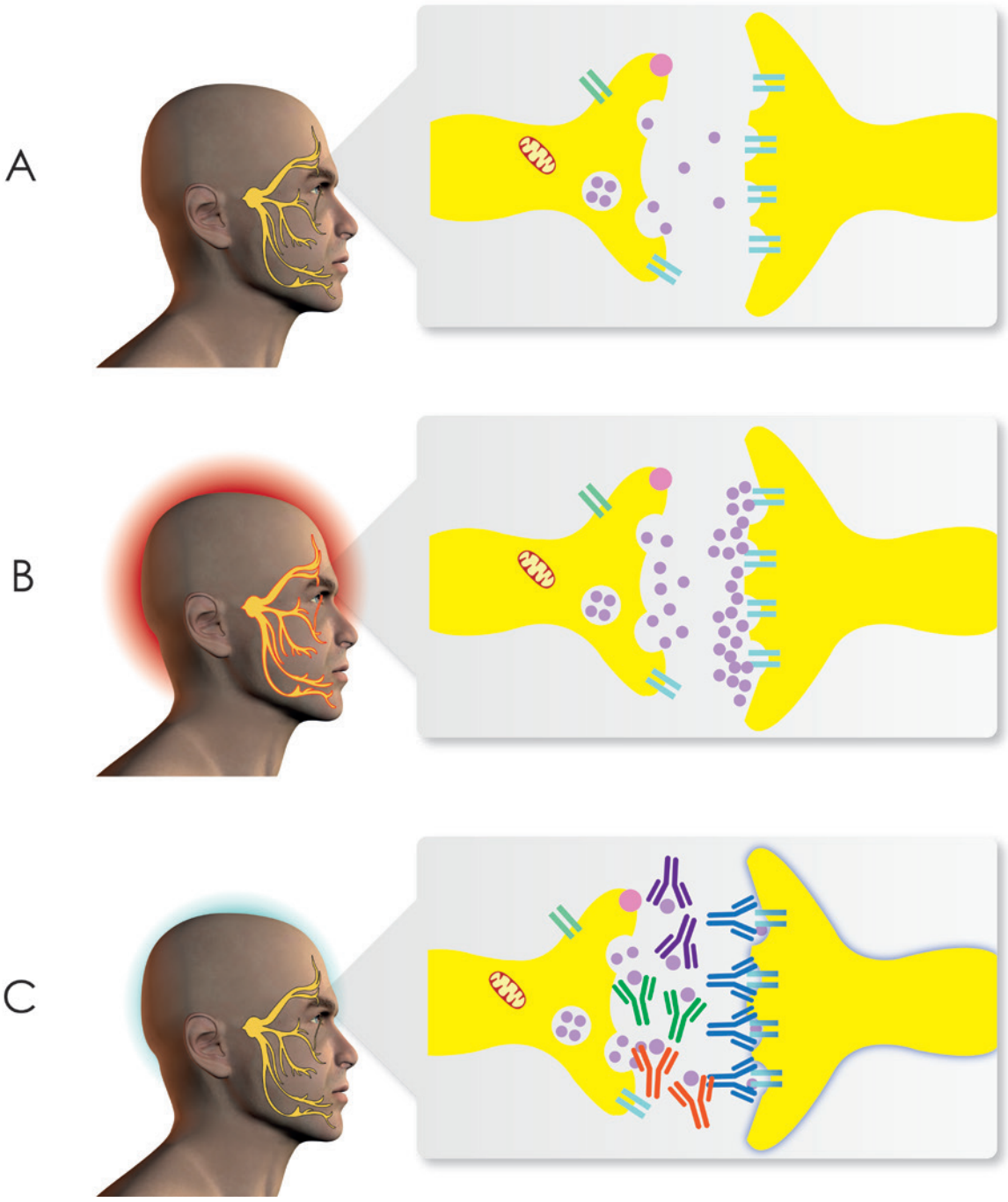
Table 1. Results of the most recently published clinical trials on the use of anti-CGRP antibodies for the treatment of migraine.

Antibody/ Clinical trial	Type of migraine	Treatment schedule	Reduction in the number of days with migraine	Reduction in the number of days of use of other drugs
Fremanezumab (TEV-48125)/ NCT02621931 Phase III	Chronic	Placebo SC every 28 days for 3 months	2.5±0.3*	1.9±0.3*
		675 mg / placebo / placebo SC every 28 days for 3 months	4.3±0.3* (p<0.001)	3.7±0.3* (p<0.001)
		675mg/225mg/225mg SC every 28 days for 3 months	4.6±0.3* (p<0.001)	4.2±0.3* (p<0.001)
Galcanezumab (LY2951742)/ NCT02614183 Phase III	Episodic	Placebo SC monthly for 6 months	2.8+	--
		120 mg SC monthly for 6 months	4.7+ (p<0.001)	--
		240 mg SC monthly for 6 months	4.6+ (p<0.001)	--
Eptinezumab (ALD403)/ NCT01772524 Phase II	Episodic	Placebo IV single dose	4.6***	--
		1000 mg IV single dose	5.6***	--
Erenumab (AMG 334)/ NCT02483585 Phase III	Episod	Placebo SC monthly for 3 months	1.8*	0.6*
		70 mg SC monthly for 3 months	2.9* (p<0.001)	1.2* (p=0.002)

* Defined as the number of days in which headache lasted >4 hours, moderate to severe intensity, or required the use of triptans or ergotamine; the results of the treatments are shown to be significantly lower compared to placebo; the follow-up was until week 12 after the first application of the treatment.
** Efficacy during the first month of treatment.
*** Efficacy between week 5 and 8 of treatment.
+ Defined as the number of days in which headache with duration >30 min occurred with both of the following clinical conditions: A (at least two characteristics: unilateral, pulsatile, moderate to severe pain and aggravation with physical activity) and B (at least one: nausea and/or vomiting and/or photophobia and phonophobia). Follow-up during 6 months of treatment and up to 5 months after the last application.
IM: intramuscular, SC: subcutaneous, IV: intravenous, NS: not significant.

Reduction in the score of functional scales	Frequency of adverse effects	Common adverse effects
4.5±0.5* (HIT-6 score)	64%	Pain, induration, erythema, or hemorrhage at the site of injection, upper respiratory tract infections, dizziness, nausea.
6.4±0.5* (p<0.001) (HIT-6 score)	70%	
6.8±0.4* (p<0.001) (HIT-6 score)	71%	
Ref (MSQ score)	60.4%	Infection of the upper respiratory tract, pain and reaction at the injection site, nasopharyngitis, nausea, pruritus.
7.7±1.3 (p<0.001) (MSQ score)	65.5%	
7.4±1.3 (p<0.001) (MSQ score)	67.7%	
--	52%	Infections of the upper respiratory tract, urinary infections, fatigue, back pain, nausea, vomiting, and arthralgia.
--	57%	
NS	54.7%	Infections of the upper respiratory tract, pain at the injection site, nasopharyngitis. Development of non-neutralizing anti-Erenumab antibodies in 4.3% of subjects.
NS	48.1%	

Figure 1. Participation of CGRP in the pathophysiology of chronic migraine and mechanism of action of monoclonal antibodies developed against said peptide. A) The CGRP is expressed in the trigeminal nerve terminals. B) In patients with migraine, the concentrations of this molecule increase during the attacks of pain, causing a dilating effect on the dural vessels and an exacerbation of nociceptive transmission mediated by glutamate. C) The monoclonal antibodies Fremanezumab, Galcanezumab, and Eptinezumab neutralize CGRP and prevent its binding to its receptor. Erenumab binds selectively to the CGRP receptor by blocking its signaling. This leads to the negative regulation of vascular mechanisms and central sensitization mediated by said peptide and its receptor involved in the pathophysiology of migraine.



(IV) or subcutaneously (SC) at a maximum dose of 2000 mg did not cause significant adverse effects nor clinically relevant changes in blood pressure, heart rate, or electrocardiogram parameters compared to placebo.[40,41] The pharmacokinetic measurements made during these studies showed a half-life of 40 to 50 days after one or two monthly doses regardless of the route of administration.[41]

Two multicenter, randomized, double-blind, placebo-controlled phase IIb clinical trials demonstrated the safety, tolerability, and efficacy of Fremanezumab for the preventive treatment of both chronic migraine and the management of high-frequency episodic migraine.[42,43] In the first study (NCT02021773), 264 subjects aged 18 to 65 years with a diagnosis of chronic migraine were randomly assigned to receive one of three treatments: placebo, Fremanezumab SC at an initial dose of 675 mg and two monthly doses of 225 mg, or 900 mg dose monthly. After three months of treatment there was a decrease in the number of hours with headache compared to the baseline level of 37.10 hours (SD 79.44) in the placebo group, 59.84 hours (SD 80.38, p=0.0386) in the group of 675/225 mg, and 67.51 hours (SD 79.37, p=0.0057) in the group of 900 mg. Likewise, there was a decrease in the number of days with moderate to severe intensity of migraine of 4.2 days (SD 6.32) in the placebo group, 6.04 days (SD 6.41, p=0.069) in the 675/225 mg group, and 6.16 days (SD 6.32, p=0.004) in the 900 mg group. Both doses significantly reduced the number of days when the use of an additional drug was necessary to relieve migraine. Adverse reactions were observed in 40%, 53%, and 47% of the subjects in the placebo, 675/225 mg, and 900 mg groups respectively. The majority was not related to the treatment and the most frequent was pain at the site of application and pruritus. No alterations were observed associated with the administration of the antibody in the normal cardiovascular parameters nor in the liver function tests.[42] In the second study (NCT02025556), the same group of researchers randomly assigned 297 individuals with episodic migraine to receive placebo, 225 mg, or 675 mg of Fremanezumab administered SC for three months. At 12 weeks after starting treatment there was a decrease in the number of days with migraine compared to the baseline of 3.46 days (SD 5.40), 6.27 days (SD 5.38, p<0.0001), and 6.09 days (SD 5.22, p<0.0001) in the placebo, 225mg, and 675mg groups, respectively. Both doses also significantly reduced the number of days with headache of any intensity and the number of days in which it was necessary to use a drug for acute pain relief, as well as days with nausea, vomiting, photophobia, or phonophobia, although the differences regarding the placebo were not spectacular. Nevertheless, both doses of the antibody significantly decreased the score on the Migraine Disability Assessment (MIDAS): 24.23 points (SD 54.56) in the group of 225mg and 24.93 points (SD 62.68) in the group of 675mg with respect to the placebo (9.73 points [SD 55.67]). The most common adverse effects were pain and erythema at the application site, reported in around 50% of all subjects. In this second group of patients, neither changes in cardiovascular parameters nor development of neutralizing antibodies against Fremanezumab were observed.[43]

Due to the documented safety in the clinical trials described, a new phase III study (NCT02621931) was conducted in a greater number of individuals with chronic headache recruited from nine countries to test the safety and efficacy of this antibody. Of 1130 subjects included in the study, only 1034 completed the trial under three different treatment regimens: 349 subjects received a single dose of 675 mg, 343 received an initial dose of 675 mg and two monthly doses of 225 mg, and 342 received placebo. The results confirmed that the antibody is effective in decreasing the frequency of migraine attacks in patients with chronic headache, since both doses of the treatment reduced the number of days with headache (>4 hours duration, moderate to severe intensity, which required use of triptans or ergotamine), the use of other drugs to treat acute pain, and the scores on the Headache Impact Test (HIT-6) scale. In addition, we observed a greater proportion of subjects who had a decrease of at least 50% in the number of days with headache at one month compared to the baseline: 38% in the group of 675 mg and 41% in the group of 675/225 mg compared with 18% in placebo (p<0.0001).

Adverse effects were reported in 64% of subjects who received placebo, 70% of those who received 675 mg, and 71% in those who received 675/225 mg (see Table 1).[38] Two other phase III clinical trials are being carried out to verify the safety and efficacy of this antibody in the management of episodic migraine (NCT02629861) and in any form of migraine (chronic and episodic, HALO study, NCT02638103); the results were not yet published at the time of writing this review.

Galcanezumab

Galcanezumab (LY2951742) is another completely humanized IgG4 antibody that binds specifically to CGRP. Like Fremanezumab, it showed inhibiting the binding of the peptide with its receptor in vitro and reversing the vasodilation induced by different stimuli in vivo. Likewise, pain was reduced with great efficacy in animal models of osteoarthritis.[44] Phase I clinical trials (NCT02576951, NCT02104765, NCT01337596) showed their safety in different groups of healthy individuals submitted to the administration of the antibody SC in single doses from 1 mg to 600 mg or multiple doses of 150 mg every two weeks, recording a half-life of 29 days.[45,46]

The first phase IIa study (NCT01625988) to test the safety and efficacy of this antibody in the prevention of episodic migraine (<14 days with pain) was performed in 35 centers in the United States, randomly assigning 218 patients to receive 150 mg of Galcanezumab SC every two weeks for 12 weeks or placebo. The primary objective of the clinical trial was the reduction induced by the antibody in the number of migraine days per month, during the last month of treatment. The study also included an additional 12-week surveillance period after the final dose. The results showed a decrease in the number of days with migraine per month from baseline to week 12 of 4.2 days (SD 3.1) in the group that received Galcanezumab and 3.0 days (SD 3.0) in the placebo group (p=0.003). Likewise, significant decreases in the number of days with headache were observed, as well as a greater percentage of responders with a decrease of at least 50% in the number of days with migraine in the group treated with the antibody with respect to placebo (70% vs 45%; OR 2.88, 90% CI 1.78-4.69). Adverse effects were reported in 72% of subjects who received Galcanezumab and 67% of those who received placebo, the most frequent being upper respiratory infections, injection pain at the site of application, back pain, arthralgia, erythema, and dizziness.[47]

A phase IIb clinical trial (NTC02163993) with this antibody for the prevention of episodic migraine was recently published in the journal JAMA Neurology.[48] This study included 410 subjects who were randomly assigned to receive placebo or one of four doses of Galcanezumab (5, 50, 120, 300 mg) SC once a month for three months. The results showed that the doses of 120 mg and 300 mg were superior to placebo in reducing the number of migraine days per month from baseline, although the 120 mg dose showed a better profile at 12 weeks of treatment, also reducing the score in the Migraine-Specific Quality of Life Questionnaire (MSQ) and the HIT-6 scale, and inducing a higher percentage of responders (reduction of at least 50% in days with pain per month) compared with placebo (75.8% vs 61.9%). (Table 1)

In the most recent study on the effectiveness of Galcanezumab for episodic migraine called EVOLVE-1 (NCT02614183), the observations of the previous investigation were corroborated, but this time with a longer follow-up period of six months and comparing the monthly dose of 120 mg and 240 mg against placebo. This work is not yet available in print but it has been published in a preliminary way on the website of the journal JAMA Neurology. Its most outstanding results are shown in Table 1. Phase III clinical trials with this antibody for the treatment of chronic migraine (REGAIN study, NCT02614261), episodic (EVOLVE-2, NCT02614196), or chronic cluster headache (NCT02397473, NCT02438826 and NCT02797951) have not yet been published.

Eptinezumab

Eptinezumab (ALD403) is a non-sialylated humanized IgG1 antibody that binds selectively to CGRP. The phase I trials that evaluated the safety and pharmacokinetic profile of this monoclonal

antibody were performed in Australia by the company Alder Biopharmaceutical, Inc. The first one was completed in April 2013 and showed that a SC or IV dose of Eptinezumab did not cause significant adverse effects in 104 participants and its half-life was 26-30 days (NCT01579383). The second study was a randomized, double-blind, placebo-controlled phase I trial. The safety of the administration of Eptinezumab was evaluated in 60 healthy volunteers who received the antibody at different doses (100 mg and 300 mg) and by several administration routes (intramuscular [IM], SC, or IV). It was observed that Eptinezumab had comparable levels of suppression of peripheral CGRP with a single monthly dose of 100 mg for 12 weeks either via IM, SC, or IV, without causing significant alterations in liver function or cardiovascular events.[49]

In a subsequent phase II study (NCT01772524) the safety, tolerability, and efficacy of Eptinezumab for the prevention of episodic migraine in adult patients was demonstrated. They randomly assigned 163 patients to receive placebo or 1000 mg of Eptinezumab IV every two weeks for 12 weeks, with an additional period of three months to evaluate the safety of the treatment. At the end of follow-up, a decrease in the number of days with migraine per month was documented at 5.6 days (SD 3.0) in the 1000 mg group compared with 4.6 days in the placebo group (SD 3.6). Adverse effects occurred similarly in both groups: 52% in the placebo group and 57% in the Eptinezumab group, the most common being upper respiratory tract infections, urinary tract infections, fatigue, back pain, nausea, vomiting, and arthralgia. Notoriously, IV administration of the antibody did not cause reactions at the puncture site.[50] Until now, the results of another phase II study started in 2014 have not been published, in which the safety and efficacy of four different doses of Eptinezumab administered IV were evaluated for the treatment of chronic migraine (NCT02275117). Two more phase III studies have already begun. The first one, called PROMISE-1 (NCT02559895), has recruited 900 subjects with episodic migraine to evaluate the quarterly administration of three different doses of Eptinezumab (30 mg, 100 mg, and 300 mg) for 24 weeks. The pharmaceutical company has announced preliminary results of 888 subjects in which it was observed that IV doses of 100 mg and 300 mg significantly reduced migraine days per month presented during the first 12 weeks of treatment in 3.9 and 4.3 days compared to 3.2 days in the placebo group (p=0.0179 and p=0.0001, respectively).[51] The PROMISE-2 study (NCT02974153) is in the phase of recruitment of patients with chronic migraine.

Erenumab

Erenumab (AMG 334) is a fully humanized IgG2 monoclonal antibody that, unlike the rest, selectively binds to the CGRP receptor in a reversible manner. In phase I studies (NCT01688739, NCT01723514) it was demonstrated that one or multiple doses of SC Erenumab inhibit dermal vasodilation induced by capsaicin, an indicator that there is an interference of the CGRP signaling pathway, without causing significant adverse effects.[52,53] The first phase II study conducted with this antibody (NCT01952574) was a multicenter clinical trial in which the efficacy of Erenumab was evaluated for the treatment of episodic migraine. We included 483 subjects who were randomly assigned to receive placebo or 7 mg, 21 mg, or 70 mg of the antibody administered SC once a month for 12 weeks. At the end of follow-up, there was a significant decrease in the number of days per month with migraine with 3.4 days (SD 0.4) in the 70 mg dose group compared with 2.3 days (SD 0.3) in the placebo group. The most common adverse effects were nasopharyngitis, fatigue, and headache both in the treatment group (95%) and in the placebo group (98%). Three percent of the treated subjects developed neutralizing antibodies against Erenumab.[54]

The second phase II multicenter study conducted with this antibody evaluated its safety and efficacy for the management of chronic migraine (NCT02066415). Erenumab 70 mg, 140 mg, or placebo was administered SC every month for three months to 667 patients. Both doses caused a significantly greater decrease in migraine days at one month (6.6 days) compared with placebo (4.2 days, p<0.0001). Likewise, 40% of the patients

who received 70 mg of the antibody and 41% in the patients who received 140 mg presented a decrease of at least 50% of the days with migraine per month three months after treatment. Adverse effects occurred with the same frequency in all groups: 39% in the placebo group, 44% in the 70 mg group, and 47% in the 140 mg group; the most common were pain at the site of application, upper respiratory tract infections, and nausea. No abnormalities were reported in vital signs, laboratory results, or electrocardiogram. Eleven subjects in the 70mg group and three in the 140mg group developed neutralizing antibodies against Erenumab.[55] A third phase II study to evaluate the safety and efficacy of the same antibody for the treatment of chronic migraine is ongoing and is a continuation of the previously described clinical trial, using the same patients but with a period of treatment and follow-up of 13 months (NCT02174861).

In the first phase III study that was recently published using this antibody (STRIVE, NCT02456740), 955 patients with episodic migraine were recruited and randomized to receive 70 mg or 140 mg of Erenumab or placebo SC every month for six months. At the end of the follow-up, the average reduction in days with migraine per month was 3.2 in the 70 mg group and 3.7 in the 140 mg group, compared with 1.8 in the placebo group. The 50% or more decrease of migraine days per month was achieved in 43.3% of patients in the 70 mg group, 50% in the 140 mg group, and 26.6% in the placebo group ($p<0.001$ for both treatment groups). The reduction in the number of days of use of specific medications for acute migraine was greater in the groups treated with Erenumab: 1.1 days for 70 mg and 1.6 days for 140 mg, compared to 0.2 days in the placebo group. The physical disability score on the Migraine Physical Function Impact Diary (MPFID) scale improved by 4.2 and 4.8 points in the group of 70 mg and 140 mg respectively, compared to 2.8 points in the placebo group. The rate of adverse effects was similar in all groups: 63% in the placebo group, 57.3% in the 70 mg group, and 55.5% in the 140 mg group. The most common adverse effects were nasopharyngitis, upper respiratory tract infections, and sinusitis. Antibodies against Erenumab were observed in 8% and 3.2% of the subjects treated with 70 mg and 140 mg, however, these antibodies were neutralizing in only one patient.[56]

Finally, the results of the most recent phase III clinical study with Erenumab called ARISE (NCT02483585), in which its effectiveness for the treatment of episodic migraine was evaluated, have been published and are summarized in Table 1. This clinical trial included 577 adults with episodic migraine who were randomly assigned to receive placebo or 70 mg of SC Erenumab monthly for three months. Although the duration of the treatment was shorter than the previous study, the effectiveness and safety of SC administration of the antibody was confirmed.[57] Another phase III study is underway to evaluate the use of Erenumab in patients with episodic migraine from other countries outside the United States and Europe (NCT03333109).

Potential risks, challenges and perspectives

The clinical trials described in this document show favorable results that support the use of the new monoclonal antibodies against CGRP or its receptor for the preventive treatment of high frequency episodic migraine and chronic migraine.[38,42,43,47,48,50,51,54-57] Due to their pharmacokinetic profile, these therapeutic agents offer the great advantage of having a long half-life, so that their monthly application would allow a better adherence to the treatment. Evidence of CGRP's role as a facilitator of pain transmission and its distribution within the central nervous system also opens up the possibility of expanding its use for other conditions in which this symptom is an important component, as in pain associated with joint inflammatory processes or other types of headache.[36,44] In fact, clinical trials are being conducted with the objective of evaluating the benefit of the use of Galcanezumab in the treatment of cluster headache (NCT02397473, NCT02438826, and NCT02797951). Likewise, a recent study in animals has shown that painful stimuli mediated by CGRP inside the lung tissue

exert an immunosuppressive effect that limits the defense responses to respiratory infectious agents, which opens the possibility of using said peptide as a new therapeutic target to improve the course of severe pulmonary infectious diseases.[58]

However, there are some areas of uncertainty that have yet to be clarified before justifying the preferential use of these antibodies over other treatments currently available. Among them, the concern arises to know the safety of the inhibition of the vasodilator responses achieved with the chronic blockade of the signaling through the CGRP receptor in different vascular beds. Although up to now no alterations in the main cardiovascular parameters have been observed, the follow-up in the clinical trials published in the literature has not been longer than one year and the phase III studies that are being carried out with a longer surveillance period (NCT02985398, NCT03303105, and NCT02959190) will not provide data on the long-term safety of the use of these antibodies, especially in populations with cardiovascular risk factors. It is probable that only phase IV studies offer such information, although being molecules with a long half-life, if a serious level of toxicity arises, it will be difficult to reverse it acutely.

The high incidence of adverse effects among the individuals treated with the different antibodies, especially those administered SC, is also a situation to be considered. Although the proportion of patients who presented an adverse effect during treatment does not differ significantly from placebo and no fatal alterations have been described, some studies describe a percentage of occurrence of up to 70%,38 with pain at the site of application as the most frequent, although in a meta-analysis it was observed that dizziness was the only symptom that occurred significantly more frequently in subjects who received some of the antibodies than in those who received placebo,[37] revealing a possible participation of CGRP in the biological mechanisms underlying this symptom.

Another relevant aspect that should be considered is the efficacy shown by the antibodies described here. Although a significantly high percentage of treated patients reduced the number of days with headache per month by at least 50% from basal level, reaching statistical significance, the net difference in this decrease induced by CGRP blockade is not spectacular since it does not exceed two days with respect to placebo in most of the studies. This efficacy is similar to that of onabotulinum toxin A, whose mechanism of action is not specific.[10,11] The development of neutralizing antibodies observed in some of the clinical trials could also limit the effect of the treatment in the long term.[54-57] In addition, it is expected that the cost of treatment will be high once the marketing of these pharmacological agents is initiated, so before they displace other therapeutic options, new cost-benefit studies should be carried out. Similarly, the widespread use of antibodies against CGRP may not improve the quality of life of all patients because there is evidence to suggest that this peptide would only play an important role in the pathophysiology of migraine in subjects with a predisposition to be sensitive to the effects of it.[27] Finally, a limitation of all the clinical trials presented in this review is that the selection criteria of the participants excluded migraine patients who had presented a poor response to other preventive pharmacological measures, who constitute the population that would probably benefit most from the treatment with antibodies. To evaluate this last possibility, clinical trials are already underway in which they intend to learn the usefulness of Fremanezumab (FOCUS study, NCT03308968) and Erenumab (LIBERTY study, NCT03096834) in the management of patients with migraine who have failed treatment with other drugs.

Conclusions

The study of the pathophysiological mechanisms of migraine and the evidence of the participation of CGRP in them have resulted in the development of four monoclonal antibodies against this peptide or its receptor, which have shown a higher efficacy than placebo in the treatment of patients with persistent pain attacks. Although presently this therapeutic possibility seems to be limited to a circumscribed universe of patients with poor response to other drugs, its use in the immediate future should be based on the analysis of the best available scientific evidence and on a cost-benefit balance in order to offer a personalized treatment to the patients most likely to improve their clinical status before displacing other measures that are still useful, since the initial cost is expected to be high. Reviews such as the one presented here provide the theoretical support to facilitate the medical practice and help health professionals responsible for the care of subjects suffering from migraine with their decision-making.

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