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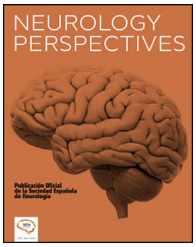

ORIGINAL ARTICLE

Description of the response to galcanezumab in 7 patients with refractory cluster headache. A review and a case series.

A.I. Dengra Maldonado*, M. Rodríguez Camacho, J.L. Ruíz Del Amo, Á. Gómez Camello

Department of Neurology, Hospital Universitario Clínico San Cecilio (Avenida del Conocimiento, s/n), 18016 Granada, Spain

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KEYWORDS
Cluster headache;
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Calcitonin gene-related peptide monoclonal antibodies;
Galcanezumab;
Trigeminal autonomic headache

Abstract
Introduction and objectives: Cluster headache is the most frequent trigeminoautonomic headache, which, together with the high impact it produces on the patient's quality of life, has led to an in-depth study of its pathophysiology, thus discovering the role of the peptide related to the gene of calcitonin and consequently test the clinical response to the functional blockade of this molecule with anti-CGRP monoclonal antibodies. We present the data of 7 patients in this regard.
Materials and methods: We describe and interpret the frequency of daily attacks of 7 patients through clinical interview, before the start, at 3, and at 6 months of treatment with galcanezumab. They are patients with refractory cluster headache, with more than 5 preventive treatments that they have used previously.
Results: Five (5) of the 7 patients (71.4%) presented a reduction in the number of attacks greater than or equal to 50% at 3 months. At 6 months, 4 of the 6 patients (66%) continue to experience a reduction in the number of attacks, 1 of them maintains unpainful and 3 of them present a reduction equal to or greater than 75% in attacks. Two patients suffered side effects that in one case led to discontinuation of treatment.
Conclusions: The response to treatment has been good, especially considering the repeatedly refractory profile of the pathology in our sample. Despite this, we accept the limitations of the study, mainly in terms of sample size and follow-up.
We provide our data on the early response to galcanezumab in patients with refractory cluster headache, which adds to the evidence that suggests that anti-CGRP monoclonal antibodies may be a valid tool and safe in the treatment of this type of patient.

* Corresponding author at: Hospital Universitario Clínico San Cecilio (Avenida del Conocimiento, s/n), 18016 Granada, Spain.
E-mail address: anai.dengra.sspa@juntadeandalucia.es (A.I. Dengra Maldonado).

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PALABRAS CLAVES
Cefalea en racimos;
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Galcanezumab;
Cefalea trigémino-autonómica

Descripción de la respuesta a Galcanezumab en 7 pacientes con cefalea en racimos refractaria: revisión y serie de casos

Resumen
Introducción y Objetivos: La cefalea en racimos es la cefalea trigeminoautonómica más frecuente, lo que, unido al alto impacto que produce en la calidad de vida del paciente, ha motivado un estudio en profundidad de su fisiopatología, descubriendo así el papel del péptido relacionado con el gen de la calcitonina y en consecuencia probar la respuesta clínica al bloqueo funcional de esta molécula con anticuerpos monoclonales anti-CGRP. Presentamos los datos de 7 pacientes al respecto.
Materiales y métodos: Describimos e interpretamos la frecuencia de ataques diarios de 7 pacientes mediante entrevista clínica, antes del inicio, a los 3 y 6 meses de tratamiento con galcanezumab. Son pacientes con cefalea en racimos refractaria, con más de 5 tratamientos preventivos que han utilizado previamente.
Resultados: 5 de los 7 pacientes (71,4%) presentaron una reducción del número de ataques mayor o igual al 50% a los 3 meses. A los 6 meses, 4 de los 6 pacientes (66%) continúan experimentando una reducción en el número de ataques, 1 de ellos se mantiene sin dolor y 3 de ellos presentan una reducción igual o superior al 75% en los ataques. 2 pacientes sufrieron efectos secundarios que en un caso llevaron a la suspensión del tratamiento.
Conclusiones: La respuesta al tratamiento ha sido buena, especialmente teniendo en cuenta el perfil repetidamente refractario de la patología en nuestra muestra. A pesar de ello, aceptamos las limitaciones del estudio, principalmente en cuanto al tamaño muestral y al seguimiento.

Introduction

Cluster headache (CH) is the most frequent trigeminoautonomic headache. It is clinically characterized by high intensity unilateral pain crises, located in the orbital, supraorbital, or temporal region, with autonomic symptoms (miosis, palpebral ptosis, conjunctival injection, tearing, rhinorrhea, nasal congestion, eyelid edema, and facial sweating), and a feeling of nervousness or restlessness. The duration of the attacks varies between 15 and 180 min, with a frequency of attacks from 1 every 2 days to 8 a day. It is a rare disorder that affects approximately 0.1% of the population,[1] unrecognized, which can lead to delay in its diagnosis and treatment. Despite its low prevalence, it is considered one of the most serious headaches due to its great impact on the patient's quality of life. CH is classified as episodic or chronic, based on the total duration of the attacks and the existence of a period of remission without crises. Pain crises usually follow a circadian pattern and are predominantly nocturnal in most cases. Episodic CH follows a seasonal pattern with pain-free periods. Three structures are involved in its pathophysiology mainly: the trigeminal-vascular system, the parasympathetic nervous system (fibers that connect in the sphenopalatine and pterygopalatine ganglion) and the hypothalamus (specifically, the suprachiasmatic nucleus). The activation of the parasympathetic fibers from the trigeminal nerve is part of the trigeminal-autonomic reflex, which gives rise to the characteristic symptoms.[1] At this time, inflammatory and vasoactive peptides are released, such as VIP (vasoactive intestinal peptide), PACAP (pituitary adenylate cyclase-activating polypeptide), CGRP (calcitonin gene-related peptide).[2] Parasympathetic neurons of the superior salivary nucleus of the pons emit nerve fibers that reach the sphenopalatine ganglion, and can trigger autonomic symptoms. Therefore, this ganglion is a potential therapeutic target. The existence of elevated levels of inflammatory peptides such as CGRP during pain attacks is also the subject of study and research for treatment in recent and coming years. Certain monoclonal antibodies against its molecule or receptor have been developed and approved for preventive treatment in migraine and episodic CH, as explained below. The hypothalamus also plays a key role in the circadian rhythm and seasonal pattern of attacks. Its regulation occurs in part by the release of melatonin from the pineal gland, which has been found to be decreased in nocturnal secretion in these patients, and is also a potential treatment. In short, hypothalamic dysfunction may be a key element in the development of this headache.[2] The treatment of cluster headache involves acute symptomatic treatment, transition treatment, and preventive treatment. The symptomatic treatment tries to stop the crisis in the acute moment, and the transitional and preventive one, to reduce the frequency, intensity, and duration of the attacks. Subcutaneous sumatriptan 6 mg, intranasal 20 mg, or intranasal zolmitriptan 5–10 mg, together with the administration of high-flow nasal oxygen (7–12 l) for 15–20 min, are the most used and effective symptomatic treatments, with a level of evidence IB.[3] The mechanism by which high-flow nasal oxygen therapy is effective is not clearly identified. It seems

that it can cause the inhibition of the activity of the neurons of the trigeminocervical complex and dural inflammation.[3] Other probably effective acute treatments described in the literature, although less used in clinical practice, or at least not the first choice due to their adverse effects, are 10% nasal lidocaine, somatostatin analogs, and ergotamine agents. Transition treatment can be the bridge between acute and preventive treatment, until the effective dose of the latter is achieved. It is a fast-acting but short-term treatment, approximately 2 weeks.[3] Among them, the most used is oral corticosteroid therapy, with progressive gradual reduction. Its potential anti-inflammatory effect can lower the levels of inflammatory peptides during pain attacks, even intervening in the synthesis of nocturnal melatonin. Its administration for a short period is not associated with adverse effects. The most commonly used dose is 60 mg of oral prednisone, with a reduction of 10 mg every 3–5 days. In recent years, anesthetic blockade of the greater occipital nerve, associated with corticosteroids, has been shown to be effective as a transitional or preventive treatment. The preventive treatments that exist are based, in general, on few clinical trials.[4] Verapamil, topiramate, melatonin, sodium valproate, and/or lithium are used as first- or second-line oral treatment. It is indicated when the patient suffers 2 or more crises daily, until he manages to be free of crises for 2 more weeks, restarting it before a new period. Verapamil is the drug of first choice due to its efficacy, safety, and lower rate of interactions, both in episodic and chronic CH, with an IA level of evidence. The mechanism of action of verapamil is not exactly known, but it is able to modulate the levels of CGRP and the circadian rhythm. Some clinical guidelines expose its possible administration up to doses of 960 mg, based on clinical trials that approved its efficacy. The most common side effect is constipation, followed by headache, bradycardia, and leg edema. In addition, it is recommended to carry out an electrocardiographic study before starting and during the dose increase. The next line of treatment if verapamil fails is lithium therapy. In clinical trials, it has been shown to be effective in reducing seizures, by at least 50%, with doses of 200 mg/12 h at the beginning and up to 800 mg/day, in a certain number of patients. However, the rate of side effects is higher and, therefore, the high frequency of discontinuation of treatment. These include gastrointestinal problems, vertigo, and the need to closely monitor kidney, thyroid, and liver function. Alternatives when the first prophylactic treatments are not effective, with a lower level of evidence and research, are topiramate (50–200 mg/day), melatonin (10 mg/day), or sodium valproate (600–2000 mg/day).[3] When oral pharmacotherapy has not achieved its objective, surgical interventions on the sphenopalatine ganglion, Gasser ganglion, vagus nerve, or greater occipital nerve may be considered. Radiofrequency ablation of the Gasser ganglion provides good results in up to 85% of patients, with a recurrence rate of 20%. The most frequent adverse effect is facial and corneal anesthesia. The trigeminal rhizotomy technique also achieves good results on seizure control, and a 20% recurrence rate.[3] Regarding peripheral neuromodulation, there is no consensus to recommend sphenopalatine nerve stimulation as a preventive treatment. Bilateral stimulation of the greater occipital nerve may also be indicated in these cases, taking into account the 11% frequency of complications (electrode migration and fracture, painful paresthesias, muscle contractures, cervical stiffness, skin pain, and infection).

In recent years, anti-CGRP monoclonal antibodies have been in the spotlight as a possible preventive treatment, since their approval and study as a preventive treatment for migraine.[3] The CGRP peptide is elevated in various locations during migraine and cluster headache pain attacks, specifically in neurons of the trigeminal ganglion and peripheral trigeminal projections. In addition, it was recently known that its infusion would induce pain crises in patients with episodic CH, and less likely in patients with chronic CH, as occurs in migraine.[4] Two recent randomized, double-blind, placebo-controlled clinical trials in patients with episodic cluster headache treated with galcanezumab, have obtained good efficacy and safety results.[5] We present below 7 patients with refractory CH and their response to galcanezumab at 3 and 6 months. The main objective was to assess the reduction in daily attacks with respect to the previous state.

Methods

Case series of 7 patients from the headache unit with a history of chronic or episodic cluster headache according to the ICDH-III classification, and without response to at least 3 first- or second-line treatments (between 1 and 8 pain crises a day despite preventive treatment). The patients were chosen based on these characteristics, to start compassionate use treatment with galcanezumab 120 mg or 240 mg injections subcutaneously once a month. The number of pain crises at 3 and 6 months from the beginning of the treatment is determined, to evaluate the individual response, by means of a clinical interview in medical consultation on headache diary data. Informed consent for initiation of treatment was also obtained from all patients.

Results

In 7 patients with refractory CH, we indicated treatment with galcanezumab, with a first dose of 240 mg, followed by 120 mg monthly. Six of the patients are men (85.7%) and one woman (14.3%). The mean age was 45 years old (s.d. 10.06) and the mean number of years since diagnosis of cluster headache was 11.14 years old (s.d. 5.08). Five patients present chronic cluster headache (71.4%) and 2 patients episodic cluster headache (28.6%). Patient had received an average of 5.58 treatments (s.d 1.9). Two of the patients had been treated years before with sphenopalatine ganglionectomy or occipital nerve stimulation. These data are shown collected in Table 1. Six (6) of the 7 patients (85.7%) were receiving other oral preventive treatments, the most frequent being verapamil.

Number of attacks at the beginning (previous treatment), at third month and sixth month during ongoing treatment with galcanezumab are illustrated in Fig. 1 for each patient. Mean attacks frequency per day prior to start of galcanezumab treatment was 4.71 attacks (s.d. 2). Mean attacks frequency per day at 3 months of treatment with galcanezumab was 2.34 (s.d. 0) and at 6 months 2.24 (s.d. 0).

Five (5) of the 7 patients (71.4%) presented a reduction in the number of attacks greater than or equal to 50% at

Table 1 Clinical and demographic characteristics of the patients included in the descriptive series.

Age	Average 45 years (±10.06)
Gender	6 men (85.7%)
	1 woman (14.3%)
Diagnosis	5 chronic CH (71.4%)
	2 episodic CH (28.6%)
Years since diagnosis	Average 11.14 years (±5.08)
Previous treatments:	5.58 treatments (±1.9)
Verapamil	7/7 (100%)
Lithium	3/7 (42.8%)
Zonisamide	3/7 (42.8%)
Topiramate	3/7 (42.8%)
Gabapentine	5/7 (71.4%)
Pregabaline	1/7 (14.2%)
Melatonine	6/7 (85.7%)
Amitriptiline	1/7 (14.2%)
Botulinum toxin	4/7 (57.1%)
Greater occipital nerve block	3/7 (42.8%)
Gangliectomy with thermal ablation	1/7 (14.2%)
Occipital neurostimulator	1/7 (14.2%)

3 months. In 3 of the 5 patients (60%), the dose was increased to 240 mg at the first medical visit. One (1) of the 5 patients (20%) was even crises free. Two (2) of the 7 patients (28%) were not 50% responder. Also in one of them, it was suspended because suffered adverse reaction.

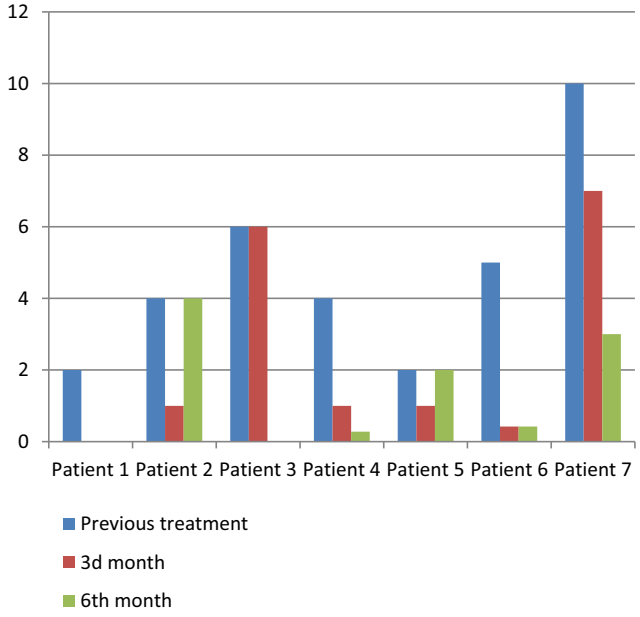

Fig. 1 Bar chart with the individual frequency of the number of seizures on the day before treatment (blue), after 3 months of treatment (red), and after 6 months of treatment (green) with galcanezumab. *Patient 3 removed the treatment on 3d month. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

At 6 months, 4 of the 6 patients who continued treatment (66%) experienced a reduction in the number of crises, 1 of them maintains a 100% response (25%) and 3 of them (75%) present a reduction equal to or greater than 75% of attacks. A progressive reduction in attacks was observed in 2 of the patients with respect to the third month. All these patients could reduce the dose of verapamil, one of them could remove of his treatment. No new medication was added during this follow-up. Two (2) of the 6 patients (33%) who experienced reduction in his pain crisis in the first 3 months before got worse after 6 months toward similar frequency to the start of treatment. These data shows in Fig. 1.

Two (2) of the 7 patients (28.5%) reported adverse effects after administration of galcanezumab. Patient 3 presented an exanthematous skin reaction in the thoracic region at third month, with spontaneous resolution, reason for discontinuation of treatment. In addittion, that patient had not experienced effect with the treatment. Patient 5 reported symptoms consistent with mild and transient flu-like syndrome.

Discussion

Galcanezumab is a humanized IgG4 monoclonal antibody which links to calcitonin gene-related peptide. CGRP is increased during attacks of pain in migraine and CH. Its infusion could generate attacks of pain. Therefore, it is a potential therapeutic target. The randomized clinical trials EVOLVE-1 and EVOLVE-2 carried out in 2016 in patients with episodic migraine during 6 months, demonstrated statistically significant and clinically relevant improvements from baseline compared to placebo, as the randomized clinical trial in chronic migrain REGAIN.[6–8] These results led to the approval of galcanezumab for FDA (US Food and Drug Administration) and EMA (European Medicine Agency) as a preventive treatment in episodic and chronic migraine since the end of 2018. Its efficacy in patients with migraine in real life is also well known and described in the literature. The FDA has approved galcanezumab (Emgality) for injection (at a dose of 300 mg) for the treatment of episodic cluster headache in adults in 2019. However, so far there are few studies describing its effect in patients with cluster headache under real-life conditions.

Our series of cases describes the response type to treatment with galcanezumab at 3 and 6 months from its start. Response rate is understood as a 50%, 75%, or 100% reduction in pain crises. The demographic characteristics of the patients are similar to those of the clinical trials. Most patients are men (85%), with a mean number of attacks per day of 4.71. Patients had received an average of 5.58 treatments (s.d 1.9), due to their situation refractory to treatment. Total number of previous preventive treatments not significantly associated with response to CGRP(R) antibody treatment, as described in the literature.[9] The observation time is up to 6 months. Data from clinical trials are up to 12 weeks.

The results in relation to the frequency of the number of attacks in daily clusters, both at 3 and 6 months, are favorable in more than half of them (66%) and the response is maintained in a half of the patients up to 6 months. This proportion of 66% responders is higher than what reported

for migraine and episodic CH (50%) with a small sample size. In addittion, 3 of the patients (50%) have experienced a reduction of more than 75% of their pain crises so far, and 1 has remained crises-free since then (100% response). It should be noted that in 2 of the patients, the reduction of the crisis is progressive with the continuation of the treatment. This fact coincided with the increased dose. In 3 of the 5 responder patients (60%), the dose was increased to 240 mg to optimize the effect at the third month; in the controlled clinical trial in patients with chronic CR, its use is described up to 300 mg,[4] although their results were not statistically significant, as detailed below.

Also, all responder patients were able to reduce the dose of verapamil and 1 of them could remove of his treatment. These patients expressed an improvement in their quality of life.

Two (2) of the 6 patients (33%) experienced improvement only during the first 3 months, after which their attacks increased in frequency. In the retrospective study of 22 patients, an increase in the frequency of attacks was also observed in 3 patients, from the first month of treatment.[9]

Two (2) of the responder patients had chronic cluster headache and another 2 had episodic cluster headache. There are studies that support the difference in treatment response between these 2 entities, due to the different chronobiology and the role of CGRP.[4] In this clinical trial, carried out between 2015 and 2019 in 12 countries, 237 patients with chronic CH were included, of whom 117 were treated with galcanezumab 300 mg. At 12 weeks, statistical analysis showed non-significant efficacy results, with a mean of 4.6 attacks per day in the placebo group and 5.7 attacks in the galcanezumab group ($p = 0.334$). The tolerability and safety of galcanezumab in this trial were consistent.[4] In the randomized clinical trial conducted by *Goadsby* et al. in 2019, 106 patients with episodic CH were included, of whom 49 received a 300 mg dose of galcanezumab. A significant result was obtained in terms of a reduction in weekly attacks to 8 compared to 5 in the placebo group, with 71% of the patients responding to 50%, with good tolerability.[5] These results led to its acceptance as a preventative therapy for episodic CR by the FDA.

In our study, 5 of the 7 (71%) patients did not present any adverse effects with the treatment, so tolerability was generally good, which is consistent with the results of clinical trials and retrospective studies. Two (2) patients (28%) reported some adverse effect. One of them presented a localized transient skin rash, for which treatment was withdrawn at the expense of being studied in an allergology consultation. This reaction, although rare, is reported as a possible side effect which could occur from the first day to 4 weeks after administration. Another patient suffered from a flu-like syndrome consisting of tiredness, low-grade fever, and headache, the day after the injection, lasting 24 h, which coincides with the most frequent adverse effects described by the drug.

There are few observational studies of treatment with calcitonin gene-related peptide monoclonal antibodies in cluster headache. In 2020, a retrospective study was carried out in Germany of a series of 22 patients with chronic CH from different headache units treated with galcanezumab 240 mg or erenumab 70/140 mg for at least 1 month. Sixteen (16) patients (73%) of 22 were treated with galcanezumab. The total number of responders was 12 of the 22 patients (55%) with a reduction of attacks greater than or equal to 50% and the use of pain medication in the first month of treatment ($p < 0.001$).[9] This percentage is maintained up to 2 and 3 months without major differences. The result is similar to what we observed in our series up to 6 months, although with a smaller sample size (7 vs 22) and without establishing statistical relationships.[9]

Conclusion

In reference to our study, it is a case series with a small sample size, and cannot provide information on the difference with placebo (under controlled conditions) to take as a proof of the preventive effect. However, it describes the experience on acting in real-life conditions and may offer a successful and safe therapeutic option in more than half of patients, at least temporarily, in populations of severely affected patients. It is considerable that the patients included had responded null or insufficiently to other treatments, with an average of 5.5 previous treatments, including botulinum toxin and surgical interventions. More clinical trials or observational studies are needed, with a larger number of samples and follow-up, that report results in patient populations refractory to other treatments and analyze the role of the CGR-peptide.

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Ethical considerations

We declare that our study was conducted according to Good Clinical Practice and the Declaration of Helsinki guidelines.

This study hasn't required the approval of the ethics committee.

Patient consent

Patients provided written informed consent before undergoing study procedures.

Author disclosures

We declare there are no conflicts of interest to report in this study.

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