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REVIEW

Reducing Episodic Cluster Headaches: Focus on Galcanezumab

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Abstract: The involvement of calcitonin gene-related peptide in migraine and cluster headache has led to the recent development of new therapies. Galcanezumab, a novel monoclonal antibody targeting the calcitonin gene-related peptide, is approved for the migraine prevention and has recently been tested for the prevention of cluster headache. Two clinical trials have been conducted to investigate the efficacy and safety of galcanezumab in episodic cluster headache and chronic cluster headache. While efficacy endpoints were not met in the chronic subtype, galcanezumab reduced the weekly frequency of attacks in patients with episodic cluster headaches. In both studies, the antibody was well tolerated. This review summarizes and critically reviews the available data regarding the rationale behind targeting the calcitonin gene-related peptide with galcanezumab for the prevention of cluster headache.

Keywords: cluster headache, calcitonin gene-related peptide, CGRP, antibody, LY2951742

Introduction

Cluster headache (CH) is a primary headache disorder characterized by recurrent and unilateral headache attacks lasting from 15 minutes to three hours.[1] Its bouts are distinguished by a striking combination of severe pain in the periorbital area accompanied by ipsilateral autonomic symptoms, such as conjunctival injection, excessive eye tearing, ptosis, nasal congestion, facial sweating, and agitation. The prevalence is about one person per 500 and is predominant in men.[2] There are two subtypes, episodic CH (eCH) and chronic CH (cCH), differentiated according to the presence and duration of periods of remission. eCH is the most common subtype, affecting up to 80% of patients[3] (Table 1, panel A). It presents as repetitive daily attacks that persist for weeks or months, followed by remission periods lasting at least three months. cCH attacks occurs for one year or longer without remission, or with remission periods lasting less than three months.[4] CH burdens individuals and society with lower work productivity and social functioning,[5,6] as well as increased health services utilization and suicidality.[7–9]

Pharmacotherapy for CH mainly focuses on terminating attacks and preventing their occurrence during recurring episodes and/or chronic periods. First-choice abortive treatments include high-flow oxygen[10] and subcutaneous sumatriptan.[11,12] Other strategies, such as intranasal triptans,[13–15] are used only if the above are contraindicated or ineffective. Prophylactic treatments are recommended in eCH patients during the active period and cCH patients. Several options are available, but they are based on a small body of evidence.[16] Of note, all prophylactic therapies are used off-label, as they are originally developed for other diseases. Suboccipital injections with corticosteroids have an established efficacy, tested in two Class I studies.[17,18] Also, neuromodulatory

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Table 1 Diagnostic Criteria and Current Pharmacological Treatments for Cluster Headache

Panel A **Diagnostic Criteria**[a]	**Panel B** **Pharmacological Treatments Used for Cluster Headache**[b]
Cluster Headache (A) At least five attacks fulfilling criteria B-D (B) Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated) (C) Either or both of the following: 1. At least one of the following symptoms or signs, ipsilateral to the headache: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhoea; eyelid oedema; forehead and facial sweating; miosis and/or ptosis 1. A sense of restlessness or agitation (C) Occurring with a frequency between one every other day and 8 per day (D) Not better accounted for by another ICHD-III diagnosis	**Acute Treatment** • Sumatriptan 6 mg (subcutaneous) • Oxygen 100% at ≥6–12 L/min (until response, or for ≥15 min) • Zolmitriptan 5 mg (nasal spray)
Episodic Cluster Headache (A) Attacks fulfilling criteria for "3.1 Cluster headache" and occurring in bouts (cluster periods) (B) At least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥3 months.	**Preventive Treatment** • Single injection or injection series with corticosteroids (suboccipital administration in the area of the greater occipital nerve) – Level A • Lithium carbonate (900 mg per day) – Level C • Verapamil (360 mg per day) – Level C • Melatonin (10 mg per day) – Level C
Chronic Cluster Headache (A) Attacks fulfilling criteria for "3.1 Cluster headache", and criterion B below. (B) Occurring without a remission period, or with remissions lasting <3 months, for at least 1 year.	

Notes: [a]Panel A is data from Headache Classification Committee of the International Headache Society (IHS).[1] [b]Panel B is data from Robbins et al.[16] We reported treatments with evidence of efficacy (Level A, B and C) in both episodic and chronic cluster headache.

strategies are utilized, including an external vagal nerve stimulator,[19,20] and the stimulation of the sphenopalatine ganglion (SPG) with a remote-controlled device surgically placed in the pterygopalatine fossa.[21,22]

In recent years, the considerable progress in migraine research and the development of new treatments targeting the calcitonin gene-related peptide (CGRP), led to a new era in migraine therapy.[23] Considering the overlapping pathophysiological mechanisms between migraine and CH,[24] anti-CGRP therapies have also been tested in CH. Galcanezumab, a humanized monoclonal antibody targeting the CGRP peptide, has been approved as a preventive treatment for episodic and chronic migraine[25,26] and more recently, as a preventive treatment in eCH.[27] Here, we review the current knowledge of CGRP in CH, along with clinical trial efficacy and safety data of galcanezumab in the treatment of CH.

Methods

A data search via MEDLINE for articles published up to February 29th 2020 was conducted. We used the search terms "galcanezumab" and "cluster headache", alone and together with the terms "calcitonin gene-related peptide" or "CGRP". Reference lists of relevant primary articles, reviews, and book chapters were also reviewed to identify any clinical and/or preclinical investigation related to the purpose of this Review that may have been missed in the search process.

Calcitonin Gene-Related Peptide (CGRP)

CGRP is a 37-amino acid peptide belonging to a family of structurally related peptides, including amylin, adrenomedullin and intermedin. It exists in two isoforms, α- and β-CGRP. The former is found in the central and peripheral nervous system, whereas β-CGRP is found mainly in the enteric nervous system.[28] CGRP is a potent vasodilator, primarily released from unmyelinated C-fibers innervating meningeal and cerebral vasculature. Once released, CGRP binds to its receptor located on myelinated Aδ-fibers and vascular smooth muscle cells.[29] Accordingly, CGRP dilates arteries and may activate nociceptive fibers, as well as provoking the release of other pain neurotransmitter, such as glutamate and substance P.[30] CGRP receptor consists of the complex of calcitonin receptor-

like receptor (CLR) and receptor activity-modifying protein 1 (RAMP1). A third membrane-associated component called receptor component protein (RCP) is necessary to ensure complete functioning of the CGRP receptor, with the activation of different intracellular pathways: 1) active recruitment of adenylate cyclase, which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), a second messenger in the cell; 2) increasing the activity of phospholipase Cβ and active recruitment of protein kinase C (PKC); 3) stimulation of protein kinase A (PKA) and activation of many transcription factors, including *c-fos*.[31] CGRP signaling pathways have been reported in the trigeminal ganglion (TG),[32] the SPG,[33] the spinal trigeminal nucleus,[34] and the hypothalamus,[35] all largely investigated in the pathophysiology of CH. In the TG, about 50% of neurons stained positive for the CGRP peptide, while the CLR/RAMP1 complex was expressed in around 35% of TG neurons and some glial cells. Co-localization of CGRP and its receptor components suggest involvement of the CGRP signaling in both neurons and glial cells.[32]

CGRP and Cluster Headaches

Clinical and pre-clinical studies implicate CGRP signaling in CH pathophysiology[36] (Figure 1). Sicuteri et al reported that salivary CGRP levels were increased in CH patients, compared to healthy subjects.[37] Also, serum CGRP from the external jugular vein was augmented during spontaneous CH attacks.[38] Additionally, CGRP level was normalized by acute treatments effective in clinical practice, but not opioids.[38] Later, human provocation studies have expedited our understanding. Sublingual glyceryl trinitrate provokes CH attack in eCH patients during the active phase.[39] It has been reported that CGRP levels increase at the peak of the provoked attack, and decrease after spontaneous or sumatriptan-induced remission.[40] Similarly, intravenous infusion of CGRP provoked CH attacks in 89% of eCH patients during the active phase.[41] CH attacks also occurred to a lesser extent (50%) in patients with cCH.[41]

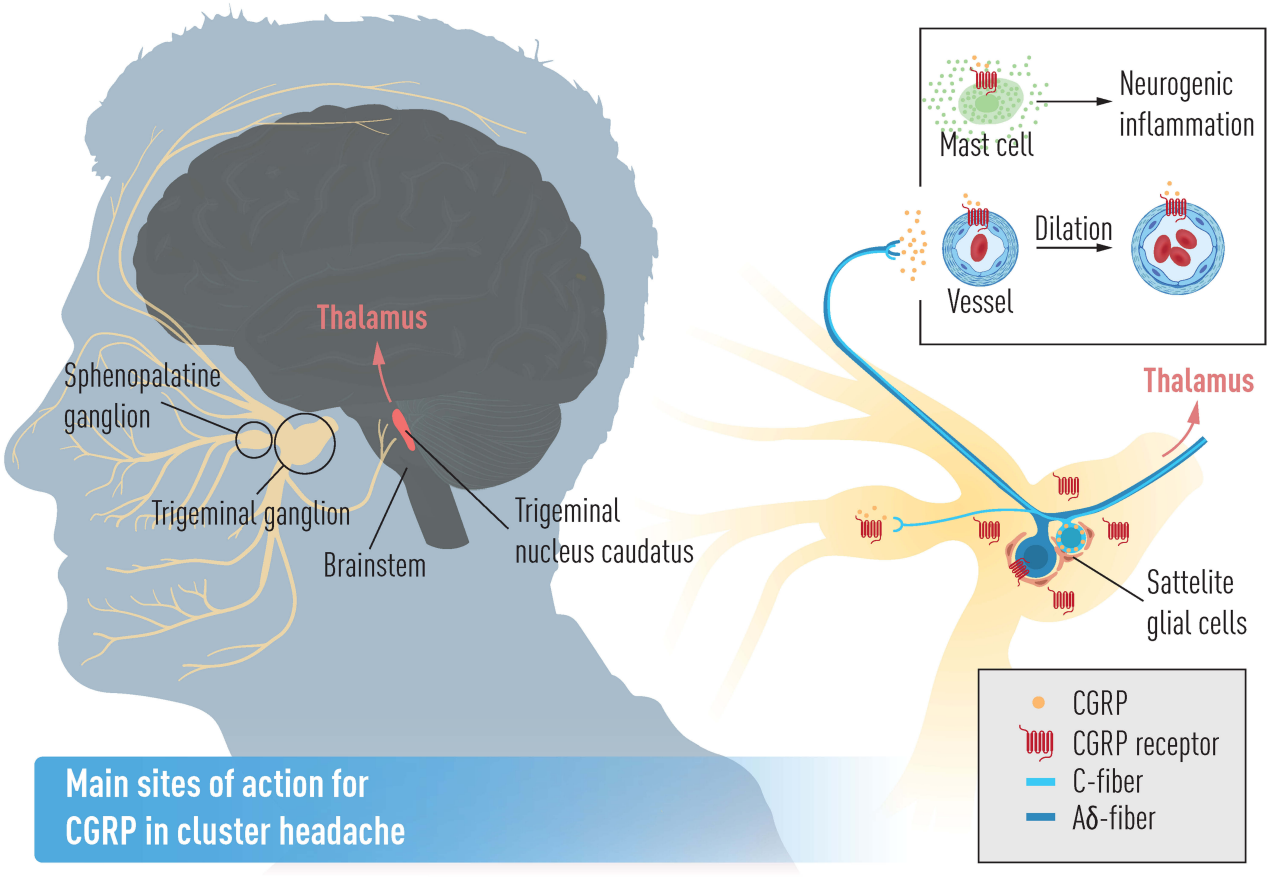

Figure 1 Main sites of action for CGRP in cluster headache. Reproduced from Belin AC, Ran C, Edvinsson L. Calcitonin Gene-Related Peptide (CGRP) and cluster headache. *Brain Sci.* 2020;10(1):30. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[36]

Pharmacological treatments for CH displayed specific interactions with the CGRP pathway. Sumatriptan, commonly used to treat acute attacks, belongs to a group of medicines called triptans, or serotonin (5-HT) receptor agonists. It acts through 5-HT_{1b} and 5-HT_{1d} receptors, expressed on the surface of the cell membrane and co-localized with CGRP in the trigeminal nerve fibers and the medium-size neurons of the trigeminal ganglion.[42] Their activation is thought to inhibit CGRP release from trigeminal neurons.[43–45] Also, oxygen, a highly effective acute treatment for CH, blocks the release of CGRP with a similar mechanism.[38] In parallel with the reduction of headache frequency, corticosteroids also decreased CGRP plasma levels in eCH patients during the active phase,[46] possibly through the blockade of a cytokine-mediated trigeminal activation.[47,48] More recently, the clinical development of galcanezumab and fremanezumab, monoclonal antibodies targeting the CGRP peptide, is in progress and has yielded results.

Galcanezumab

Galcanezumab is a highly specific and potent humanized immunoglobulin G monoclonal antibody targeting the CGRP peptide.[49] Currently, it is approved for the prevention of episodic and chronic migraine in the United States, Canada, United Kingdom and several European countries.[25,26,50] Patients can self-inject galcanezumab as subcutaneous formulation, marketed as Emgality. More recently, the antibody has also been studied for the preventive treatment of CH. As of June 2019, it has been approved in the US for the prevention of eCH. CH dosing is different from the migraine dosing. The recommended dose of galcanezumab for CH is 300 mg at the onset of the cluster period, and once a month until the end of the active phase.

Pharmacokinetics

Galcanezumab exhibits dose-linear pharmacokinetics, with a direct proportionality between doses and exposure.[51] Dosing adjusted for body weight is not warranted and patient factors, such as age, sex, ethnicity and injection-site location do not affect its pharmacokinetics.[51] Due to its large size, low permeability through cell membranes and instability in the gastrointestinal tract, it is parenterally administered in the arm, thigh or abdomen, either with a pre-filled syringe or an auto-injector.[52] The absorption is slow, with a time to peak concentration in the second week after administration. The apparent volume of distribution is 7.33 liters, whereas the half-life is 27 days.[53] Galcanezumab is eliminated by either excretion or catabolism in smaller peptides and amino acids,[54] and not in the urine. Its administration in single doses (1–600 mg) and consecutive doses (150 mg) was well tolerated in healthy male volunteers.[51] There was no apparent difference between galcanezumab groups or between galcanezumab and placebo in terms of type and frequency of adverse events (AEs), or changes in vital signs, electrocardiographic parameters and laboratory values. The most common AEs were headache, nasopharyngitis, dermatitis and diarrhea. All of them were transient with no apparent relationship with the prolonged systemic drug exposure.

Mode of Action

Galcanezumab binds and neutralizes the CGRP ligand with high affinity. Thus, galcanezumab inhibits CGRP-mediated induction of cAMP and capsaicin-induced dermal blood flow (DBF).[49] The latter represents a usable pharmacodynamic model in vivo to assess the "scavenging" of CGRP. The model consists of the topical application of capsaicin on the skin, which activates the transient receptor potential vanilloid 1 (TRPV1) channels expressed by primary sensory neurons. This activation results in the release of CGRP, a pivotal mediator of capsaicin-induced DBF. Moreover, neutralization of CGRP significantly reduced pain behavior in a prolonged and dose-dependent manner, independently of prostaglandins.[49] In humans, blockage of CGRP in single doses and consecutive doses was also consistent with a robust, dose-dependent, and durable inhibition of capsaicin-induced DBF.[51]

The site of action of galcanezumab is still a matter of debate. CGRP receptors are well expressed in peripheral tissues and the central nervous system (CNS).[55] However, human antibodies, including IgG, cannot easily penetrate the blood-brain barrier (BBB).[56] Moreover, there is no evidence suggesting disruption of BBB in CH. In rats, galcanezumab infusion reached its highest concentration in plasma, spleen, dura and trigeminal ganglion.[57] Penetration into the CNS was very low, ranging from 0.1–0.3% of the plasma concentration.[57] Collectively, these data suggest that galcanezumab is likely to act in the periphery.

Galcanezumab in Cluster Headaches

Assessment of Primary and Secondary Outcomes

Efficacy of galcanezumab in eCH patients has been investigated in a single clinical trial.[58] An 8-week, double-blind, placebo-controlled study was conducted at 35 sites in

Europe and North America (Table 2). 106 patients were randomized to receive a single injection of subcutaneous galcanezumab at a dose of 300 mg or placebo, at baseline and at 1 month. All patients were allowed to use traditional abortive treatments, including triptans, oxygen, paracetamol and nonsteroidal anti-inflammatory drugs. At the baseline, patients complained 17.8 attacks per week in the galcanezumab group, compared with 17.3 in the placebo group. Across weeks 1 through 3, the galcanezumab group benefited 8.7 fewer weekly attacks compared to baseline, respect to 5.2 fewer weekly attacks in the placebo group. Also, the proportion of patients with ≥ 50% reduction in weekly attacks at week 3 was 71% in the galcanezumab group, significantly higher when compared to placebo (53%). For other secondary endpoints, the findings were consistent with the direction of the effect for the primary endpoint measure, with a larger effect in the initial weeks of the double-blind phase. After week 4, the reduction of the weekly attacks in the galcanezumab group and the placebo group converged. Spontaneous improvement or remission may have occurred, according to the natural course of the disease. In cCH patients, galcanezumab failed to meet both primary and secondary endpoints.[59] A total of 237 patients were randomized to monthly subcutaneous injection of galcanezumab (300 mg) or placebo, for 12 weeks (Table 2). The mean reduction in weekly attack frequency, as well as the mean percentage of patients with ≥ 50% reduction in weekly attacks across weeks 1–12 was not different between groups. Also, there was no difference in acute treatment use between galcanezumab and placebo.[60] An open-label extension study (NCT02797951) evaluating the long-term safety and tolerability of galcanezumab administered in participants with eCH and cCH is expected to end in 2020.

Assessment of Adverse Events

The safety of galcanezumab was consistent among patients with migraine, eCH and cCH patients.[58,59,61–63] Most AEs were rated mild to moderate in intensity, without any relationship with the prolonged half-life of the antibody. The most frequently treatment-related AEs were injection-site pain, nasopharyngitis and other injection-site reactions. Injection-site pain was the most common,[58] reported from 8% of the patients who received galcanezumab compared with none in the placebo group. Discontinuation due to AEs resulted in 4% of the patients treated with galcanezumab, compared with 2% who received placebo. Vital signs, laboratory analyses and electrocardiographic variables were not different between the two groups. There is no evidence that the safety profile of galcanezumab is similar in more vulnerable patients, including those with cardiovascular diseases and other risk factors, including

Table 2 Galcanezumab Trials for eCH and cCH Prevention

	Study Population	Dose and Frequency	Main Endpoints	Primary Results	Key Secondary Results
Episodic cluster headache[65]	Galcanezumab: 49 Placebo: 57	Two administrations (baseline and month 1) of galcanezumab 300 mg s.c. or placebo s.c.	Primary Mean change from baseline in the weekly frequency of CH across week 1 through 3 Key secondary Percentage of patients with a reduction of at least 50% in the weekly frequency of CH at week 3	Galcanezumab: −8.7 ± 1.4 Placebo: −5.2 ± 1.3 (p = 0.040)	Galcanezumab: 71% Placebo: 53% (p = 0.046)
Chronic cluster headache[66]	Galcanezumab: 117 Placebo: 120	Three administrations (baseline, month 1 and month 2) of galcanezumab 300 mg s.c. or placebo s.c.	Primary Mean change from baseline in weekly frequency of CH across weeks 1–12 Key secondary Mean percentage of patients with at least 50% reduction from baseline in the weekly attack frequency across weeks 1–12	Galcanezumab: −5.4 Placebo: −4.6 (p = 0.334)	Galcanezumab: 32.6% Placebo: 27.1% (p = 0.170)

Note: Primary endpoints were reported as mean ± standard deviation, except for chronic cluster headache.[66]
Abbreviations: eCH, episodic cluster headache; cCH, chronic cluster headache; s.c., subcutaneous; AEs, adverse events.

smoking. CH is prevalent in middle-aged and older men, when the risk of cardiovascular disease is increased.[64] Also, some risk factors, such as smoking, are more prevalent in CH.[65] Unfortunately, current results from clinical trials are inconclusive, CH patients with serious diseases or significant cardiovascular risks were excluded on account of the study criteria.[58,59] Data from sources other than traditional trials, including real-world data, are accordingly required to clarify matters. Another concern for the safety of galcanezumab is the emergence of anti-drug antibodies (ADAs). Such emergence is correlated with possible allergic reactions, and low efficacy in several disorders.[66] As far as we know, no patient had a positive result for ADAs during the double-blind period of the single study conducted in eCH patients.[58] In the cCH study, treatment-emergent ADAs appeared only in one galcanezumab-treated patient, with no further complications.[59] The limited use and the discontinuation of the antibody shortly after patients are out of the cluster period may be helpful in limiting the emergence of neutralizing antibodies and their negative implications.

Future Perspectives

CH is an extremely painful and debilitating headache disorder. Only a few preventive therapies are currently available, in many cases with limited efficacy or poor tolerability (Table 1, panel B). Galcanezumab is the first FDA-approved drug for the reduction of CH attacks in patients with eCH in the active phase.[67] The approval was issued in US and in some other countries, whereas the Committee for Medicinal Products for Human Use of European Medicines Agency considered a single study not robust enough for regulatory endorsement in Europe. In patients with cCH, galcanezumab was not effective. Interestingly, CGRP infusion provoked CH attacks very frequently in eCH patients during the active phase, but CGRP-provoked attacks were less frequent in patients with cCH.[41] Accordingly, the lack of efficacy of anti-CGRP antibodies in cCH patients might be related to a less hypersensitivity to CGRP-induced attacks. Of interest, no headache attacks were reported after CGRP infusion in patients with eCH, in remission.[41] Compared to the other subgroups of CH patients, eCH patients in remission displayed higher baseline levels of CGRP.[68] Also, the lack of effect of galcanezumab parallels the poor treatment response in patients with cCH,[69] that are more treatment resistant than patients with eCH.[70]

A separate investigation in patients with CH has also been conducted with fremanezumab, a different antibody targeting the CGRP peptide. Its clinical development programme, which also included a long-term safety study, was suspended after futility analyses found that the primary endpoint would not be met in either patients with eCH (NCT02945046) and cCH (NCT02964338). To date, no data are published and therefore cannot be discussed.

New data on galcanezumab and CH are coming in, including the 52-week open-label extension study in chronic patients.[59] Further information is also pending from the clinical practice in patients with eCH, in terms of effectiveness, safety and tolerability. As example, any new adverse event associated with the blockade of physiological functions of CGRP and/or the repeated, albeit short-term, use of galcanezumab in eCH. Monitoring for cardiovascular function and immunogenicity is also desirable, as is safety in certain vulnerable populations, including individuals over 65 years, pregnant and/or breastfeeding women.

Abbreviations

5-HT, serotonin; 5-HT_{1b}, serotonin receptor 1B; 5-HT_{1d}, serotonin receptor 1D; ADAs, antidrug antibodies; AEs, adverse events; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; cCH, chronic cluster headache; eCH, episodic cluster headache; CGRP, calcitonin gene-related peptide; CH, cluster headache; CLR, calcitonin receptor-like receptor; DBF, dermal blood flow; FDA, Food and Drug Administration; PKC, protein kinase C; RAMP1, receptor activity-modifying protein 1; RCP, receptor component protein; SPG, sphenopalatine ganglion; TRPV1, transient receptor potential vanilloid 1; US, United States.

Author Contributions

Each author made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed on the journal to which the article will be submitted; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage; as well as agree to be accountable for all aspects of the work.

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