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RESEARCH ARTICLE

Calcitonin Gene-Related Peptide Monoclonal Antibodies for Cluster Headache

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ABSTRACT

Cluster headache is a disabling neurologic disorder that is characterized by daily, attacks of very severe, strictly unilateral pain occurring over a period of weeks or months. Recently, calcitonin gene-related peptide and its receptor complex have garnered attention as promising targets for treating primary headache disorders: particularly migraine and cluster headache. Calcitonin gene-related peptide is found in the trigeminal sensory innervation of major cerebral vessels thought to carry nociceptive information during a headache. Increased levels of calcitonin gene-related peptide have been seen in the ipsilateral jugular venous outflow during an attack phase, and indeed, calcitonin gene-related peptide itself can trigger an attack if administered to a patient in bout, suggesting its distinct role in the generation of attacks. Various monoclonal antibodies targeting calcitonin gene-related peptide and its receptor are emerging as a new frontier in migraine with potential further therapeutic use in cluster headache. This review summarizes the current therapeutic approaches of cluster headache before sharing the potential future role of calcitonin gene-related peptide and its relevance in cluster headache pathology and as targets for future treatment.

Introduction

Cluster headache is a well-characterized, disabling primary headache disorder that affects 0.05-0.1% of the population with a typically higher male preponderance[1-3]. Cluster headache is recognized by attacks of severe, strictly unilateral head pain, associated with ipsilateral cranial autonomic symptoms and/or with restlessness and agitation[4]. Attacks range from occurring once every other day to eight times daily and on average, last 15 to 180 minutes when untreated[4]. Cluster periods are separated by attack-free remissions of variable duration, dependent on whether the patient has episodic or chronic cluster headache[4]. Episodic cluster headache is defined as having at least two cluster periods lasting from seven days to one year, when untreated, separated by an attack-free remission of at least three months[4]. Patients with episodic cluster headache account for 85-90% of patients with cluster headache[4]. The disease burden of cluster headache is substantial, with patients reporting impairments in their day-to-day functioning, ability to work[5,6] and some even reporting suicidal ideation in periods of attacks[7]. Existing treatments for cluster headache remain insufficient, with the majority of medications used having a diverse range of side-effects, contraindications and varying levels of effectiveness[8].

Calcitonin gene-related peptide (CGRP) is a potent vasodilatory, pro-inflammatory signalling molecule present in both the central and peripheral neurons of the nervous system[9]. It was discovered more than forty years ago when alternative processing of RNA transcripts from the calcitonin gene predicted a product other than calcitonin[10]. Following its discovery, CGRP has been extensively investigated for its role in primary headache disorders, albeit with the majority of studies focusing on its role in the pathophysiology of migraine[11,12]. There are two major isoforms of CGRP, α-CGRP and β-CGRP, which differ by three amino acids[13]. The isoforms are synthesised from two distinct genes at different sites on chromosome 11 in the human[14,15]. Tissue-specific alternative mRNA splicing of the calcitonin gene (CALC I) produces α-CGRP, whilst β-CGRP is exclusively formed from a separate CALC II gene[16]. Over the last decade, CGRP antagonism, via the use of receptor antagonists and monoclonal antibodies targeted against CGRP or its canonical receptor, has shown to be efficacious in preventing migraine[17].

Considering that cluster headache shares pathophysiology with migraine through cranial nociceptive structures, it is likely that CGRP plays a role in the mechanisms underlying cluster headache. Early studies by Goadsby and Edvinsson observed elevated levels of CGRP and vasoactive intestinal polypeptide (VIP) within the external jugular vein in patients with acute spontaneous cluster headache attacks, which subsequently normalized with successful headache treatment[18]. It has additionally been shown to increase following induction of cluster headache attacks using systemic nitroglycerin administration[19], and indeed, CGRP itself can trigger attacks in individuals with an active disease phase[20]. The above findings clearly support the role of CGRP in cluster headache and as such, it is logical to expect that anti-CGRP therapies have been tested for the treatment of cluster headache. Out of the four monoclonal antibodies that target CGRP or its canonical receptor, galcanezumab has been approved as a preventive treatment for episodic cluster

headache[21]. Herein, we review the current literature and understanding of CGRP in cluster headache alongside the clinical trial evidence for monoclonal antibody use in patients with cluster headache.

Current therapeutic approaches of cluster headache

The European Academy of Neurology has recently published guidance regarding the standard-of-care treatment for cluster headache[22]. Treatment for cluster headache is separated into acute attack management focused on aborting the individual attack, and preventive therapy which aims to prevent or suppress attacks during the cluster period[23].

Acute attack treatment

The widely-accepted primary management for the treatment of acute cluster headache attacks consists of high-flow oxygen 100%, administered at a minimum rate of 12 L/min for at least 15 minutes, alongside the potential use of triptans[22]. Oxygen stands out as a highly effective therapy, with 78% of patients noting significant pain relief after 15 minutes[24,25]. It has no cardiovascular limitations, can be used multiple times daily with no risk of toxicity and has minimal side effects[25]. Equally, there is high-level evidence for the use of triptans in cluster headache attack management[23]. In a multicentre, double-blind, randomized crossover study, the efficacy, safety and tolerability of subcutaneous sumatriptan (6 mg and 12 mg) was evaluated and concluded that headache relief was reported in 49% of patients using the 6 mg sumatriptan injection and 63% of those using the 12 mg injection within 10 minutes[26]. This further increased to 75% (6mg) and 80% (12 mg) of patients within 15 minutes[26]. Whilst subcutaneous sumatriptan remains the most effective, various other formulations have proved beneficial including intranasal sumatriptan 20 mg (responder rate 57% vs placebo 26%)[27], intranasal zolmitriptan 5 and 10 mg (responder rate 5 mg 40-50% vs 10 mg 62-63.3% vs placebo 21-30%)(28, 29) and oral zolmitriptan 10mg in episodic cluster headache only (responder rate 47% vs placebo 29%)[30]. However, triptan use is limited by daily intake, increased adverse events and contraindications including untreated arterial hypertension as well as cardio- and cerebrovascular disorders[25]. Other acute drug therapies for cluster headache include lidocaine, ergotamine derivatives and octreotide[22]. Non-invasive vagal nerve stimulation (nVNS) is the only identified neuromodulation device that has been used in the acute treatment of cluster headache[31]. Two blinded, sham-controlled studies (ACT1 and ACT2), involving a total population of 253 patients, demonstrated significant therapeutic benefits for the episodic cluster headache cohorts of both ACT1 (active, 34.2%; sham, 10.6%; P=0.008)(32) and ACT2 (active, 48.0%; sham, 6.0%; P<0.01)[33], but not for the total populations or chronic cluster headache cohorts[31-33].

Preventive treatment

For preventive therapy, verapamil remains the medication of choice for both episodic and chronic cluster headache[22]. The efficacy of verapamil is accepted, if not well-supported in the trial literature, and it is well-regarded by many patients[34]. A double-blind placebo-controlled study demonstrated that verapamil significantly reduces attack frequency (verapamil 0.6 ± 0.88, placebo 1.65 ± 1.01; P < 0.001) and the consumption of analgesics (verapamil 0.5 ± 0.87, placebo 1.2 ± 1.03; P <

0.004)[35]. Verapamil is generally well-tolerated, however, to be of benefit, patients must take high doses, typically twice that of cardiovascular doses[36], resulting in common adverse effects, such as cardiac rhythm abnormalities seen in 19-38% of patients as well as constipation, lower limb oedema, fatigue and gingival hyperplasia[37-39]. Lithium is a second-line preventive[22]. It is less effective than verapamil in reducing headache index (lithium 37% vs verapamil 50%), whilst patients experience more side-effects (lithium 29% vs verapamil 12%) and have to undertake stringent monitoring of serum lithium levels[40]. Topiramate may also be offered as a second-line preventive[22], however, use is commonly associated with cognitive impairment and more seriously, with risk of suicidal thoughts and behaviour[41]. If first and second-line preventives are ineffective, contraindicated or discontinued, other therapeutic drugs, such as melatonin, and dihydroergotamine , may be used[21,22].

Transitional therapy

Transitional therapy with corticosteroids or frovatriptan may be considered as a short-term preventive treatment that bridges the time until preventive medication becomes effective in those with an active bout of episodic cluster headache and chronic cluster headache[22]. Sufficient data does not exist on the right time to start long-term preventive therapy[22]. Corticosteroids, given orally, intravenously or injected into the peri-greater occipital nerve area, is the most favourable bridging therapy with evidence that a single dose of oral prednisolone produces a short-term improvement [42]. Similarly, a single dose of intravenous methylprednisolone (MPD) has been shown to reduce attack frequency (*n*=13, before MPD: 1.38 ±0.42 and after MPD: 0.83 ± 0.78; *P* = 0.05 Student's *t*-test)[43]. Although single doses of steroids can invariably disrupt attack frequency, it was observed that 77% of patients had attack recurrence within seven days following single-dose MPD, suggesting that single doses are ineffective at maintaining complete headache remission [43]. In contrast, a short-term reducing regime of oral prednisolone, added to verapamil, given over a total of 17 days in patients with active episodic cluster headache has found to reduce attack frequency compared to that of the placebo group (difference −2·4 attacks, 95% CI −4·8 to −0·03; *P*=0·002) [44]. Unsurprisingly, the steroid course given was linked to a high adverse effect profile with 71% (37/52) of patients taking prednisolone reporting headache, palpitations, dizziness and nausea[44]. Superior to oral and intravenous steroid administration, greater occipital nerve (GON) blocks offer short-term preventive treatment for cluster headache, with one systematic review finding a significant response in one or more of frequency, severity and duration of individual cluster headache attacks (47.8-100%) across a sample of 22 studies (2 RCTs, 8 prospective, 8 retrospective, 4 case reports)[45]. Adverse effects were reported as mostly transient and self-resolving, except for potential avascular necrosis of the hip, injection site cutaneous atrophy and alopecia, and can be minimised by using methylprednisolone as the chosen choice of steroid[45].

The next step

Considering that cluster headache is an extremely painful headache disorder with treatment options, both acutely and preventively, limited by lack of efficacy or adverse effects,

there is a substantial need for new therapeutic approaches, one of which is the potential use of monoclonal antibodies targeted against CGRP or its receptor. Following the successful transition from laboratory to licensed medication in preventive migraine therapy, CGRP and the CGRP receptor have taken centre stage as therapeutic targets for primary headaches[46]. CGRP levels are elevated in active cluster headache periods[18] and CGRP, itself, can trigger attacks when administered systemically[20]. Clinical trials investigating the use of monoclonal antibody therapy have produced unexpected results, with galcanezumab being reported as effective and well-tolerated for the preventive treatment of episodic cluster headache[47], whilst in chronic cluster headache, there was no difference observed between galcanezumab and placebo[48]. Likewise, clinical trials of fremanezumab were recently terminated in both episodic[49] and chronic cluster headache as a result of failure to meet its primary endpoints[21]. Erenumab has not been FDA-approved as preventive cluster headache therapy, however, may be tested off-label for this[11]. Recent clinical trials investigating erenumab (CHERUB01, NCT04970355) and eptinezumab (ALLEVIATE, NCT04688775 and CHRONICLE, NCT05064397) have been completed, with no results published to date.

Calcitonin Gene-Related Peptide Physiology

CGRP belongs to a small family of structurally related peptides which include calcitonin, amylin, adrenomedullin (AM) and adrenomedullin 2 (intermedin, AM2)[50]. It is a potent vasodilator that is found in unmyelinated sensory C-fibers and myelinated AΔ-fibers commonly associated with vasculature[51]. Within the C-fibers, it colocalizes with other peptides in the C-fibers, including SP[52]. CGRP is abundant in the body and occupies both the central and peripheral nervous systems, extending to areas such as the striatum, amygdala, hypothalamus, thalamus, brain stem and is present at all spinal levels[53]. It is particularly prominent in the trigeminovascular system, with the highest concentration of CGRP being measured in the trigeminal ganglia[54]. Studies investigating CGRP immunoreactivity have found that all regions of the cerebral cortex as well as all cortical neurons positive for CGRP, with further specific labelling showing that CGRP resides mainly in the cell somas, located in cortical layers II-VI[55]. Further retrograde fluorescent tracing combined with immunocytochemistry demonstrates the widespread innervation targets of individual trigeminal cells, revealing that approximately 32% of trigeminal ganglion cells containing CGRP project to the cerebral vasculature in contrast to the forehead (12%), mandibular branch (21%) and entire ganglion (23%), respectively[56]. The close association of ganglion cell bodies innervating the cerebral vasculature as well as other targets may underlie the convergence of their central processes onto common brain-stem trigeminal nucleus cells and explain the referral of headache pain[57].

The release of CGRP occurs in response to the activation of sensory nerve fibers, either via activation of transient receptor potential (TRP) channels, mainly TRPA1[58], or by electrical, chemical, thermal and mechanical stimulation [50,59,60]. This triggers the depolarisation of pseudounipolar sensory neurons, whose cell bodies lie peripherally in the trigeminal ganglia and project centrally into the spinal trigeminal

nucleus (STN) of the brainstem and into the C1/C2 levels of the spinal cord[61]: the trigeminocervical complex[62]. This activation stimulates calcium-dependent exocytosis, mediated by members of the SNARE (soluble N-ethymaleimide-sensitive factor attachment protein receptor) protein family[63]. As a result, CGRP is released from perivascular sensory trigeminal nerve endings where the CGRP precursor protein undergoes proteolytic cleavage and the addition of a COOH-terminal amide group, making it suitable for ligand-receptor interaction[64].

The actions of CGRP are then mediated through predominantly the canonical CGRP-receptor complex, formed by the calcitonin receptor-like receptor (CLR), receptor activity modifying protein (RAMP1) and receptor-component protein (RCP)[65]. Further *in vitro* studies suggests that CGRP may interact with other non-canonical receptors, such as the amylin (AMY_1) receptor[66] and the adrenomedullin receptor (AM_2)[67]. For the focus of this review, we have concentrated on the receptor physiology of the canonical CGRP-receptor complex. CLR, when presented as a heterodimer with RAMP1 at the cell surface, which functions as a CGRP receptor. The C-terminus of CGRP is captured by the N-domain of the receptor with high affinity, whilst the N-terminal of CGRP binds to the juxtamembrane region, which in turn, activates the receptor and stimulates intracellular signalling, enhanced by receptor component protein (RCP)[68,69]. Downstream, the canonical CGRP-receptor complex is coupled to favourably Gαs and, less favourably Gαq, to execute its physiological functions, such as vasodilation[70]. CGRP results in the $G_S\alpha$-mediated activation of adenylate cyclase (AC), resulting in the sequential production of cyclic adenosine monophosphate (cAMP)[71] and downstream activation of protein kinase A (PKA), which facilitates phosphorylation and the opening of potassium (K_{ATP}) channels (50). CGRP is then able to hyperpolarise arterial smooth muscle, resulting in vasodilation. This has shown to be partially reversible in the presence of glibenclamide, a K_{ATP} channel antagonist, in rat pial arteries[72]. Although vasodilation in response to CGRP occurs as an endothelium-independent mechanism in the majority of tissues[73], there is additional evidence for a nitric oxide-dependent mechanism, by which CGRP in the presence of an intact endothelium results in a significant rise in both cAMP and cGMP[74], which stimulates endothelial nitric oxide synthase (eNOS) activity and leads to the increased synthesis and release of nitric oxide, causing vasodilation[75,76].

Calcitonin Gene-Related Peptide and Cluster Headache

Direct evidence for human *in vivo* trigeminovascular activation in cluster headache was first observed by Goadsby and Edvinsson in 1994 who found significant increases in the levels of CGRP, which marks the trigeminovascular system, and VIP, which marks parasympathetic activity, in the external jugular veins of patients with acute attacks of cluster headache[18]. It is now well-established that the trigeminal-autonomic reflex, consisting of the afferent trigeminal nerve and the efferent facial/greater superficial petrosal nerve (parasympathetic) dilator pathway, is prominently activated in attacks of cluster headache, accounting for the rises observed in various neuropeptides[77]. The trigeminal-autonomic reflex is mediated by the cranial parasympathetic outflow through a

hexamethonium-sensitive classical autonomic synapse[78,79] with functional activation through, at least, the sphenopalatine and otic ganglia[18,80]. The cells of origin for the cranial parasympathetic outflow arise in the superior salivatory nucleus in the pons[81], which can be activated with stimulation of a trigeminovascular nociceptive input, such as that from the superior sagittal sinus[82]. Once activated, it stimulates vasodilation of cranial arteries by the release of vasodilatory neuropeptides, including CGRP, VIP and pituitary adenylate cyclase activating polypeptide (PACAP)[18,83].

Given the clear involvement of CGRP in cluster headache pathophysiology, newer studies have investigated the role of CGRP and other neuropeptides in the initiation of a single cluster headache attack. A randomized, double-blind, placebo-controlled, two-way crossover study demonstrated that intravenous infusion of CGRP induced cluster headache attacks in 8 of 9 episodic cluster headache patients in the active phase (mean, 89%; 95% CI, 63-100) compared to 1 of 9 in the placebo group (mean, 11%; 95% CI, 0-37; $P=0.05$). Similarly, CGRP induced attacks in 7 of 14 patients with chronic cluster headache (mean, 50%; 95% CI, 20-80) compared to none in the placebo group ($P=0.02$)[20]. No attacks in patients with episodic cluster headache in remission were able to be provoked[20]. The study demonstrated that CGRP was a trigger of individual cluster headache attacks in active phases of the disorder, as opposed to remission[20]. The authors shared three distinct possible mechanisms for the triggering effects of CGRP[20]: the first, via neurogenic inflammation[84]; the second, that CGRP receptor components are found in the human trigeminal ganglion, hypothesized as the site of action for CGRP receptor antagonists[85,86] and the third, that neurons in the sphenopalatine ganglion express CGRP and its receptor components[87], stimulating the parasympathetic efferents, thereby activating the trigeminal-autonomic reflex[88].

Interestingly, one study compared the serum neuropeptide levels of patients with cluster headache and found that at baseline, patients with episodic cluster headache in remission had the highest levels of CGRP, compared to those in bout and those with chronic cluster headache, whilst PACAP38 levels were highest amongst those with episodic cluster headache in bout[89]. No difference was seen amongst baseline levels of VIP between cluster headache groups[89]. Serum CGRP levels were additionally compared to migraine patients and healthy controls and it was found that all cluster headache patients, irrespective of disease phase, had higher levels of plasma CGRP[89]. The differences in neuropeptide levels amongst cluster headache patients suggest that plasma CGRP may fluctuate with disease activity, indicating basic pathophysiological differences between phenotypes of cluster headache[89]. The authors hypothesize that secreted CGRP may act to further increase CGRP release in a positive feedback loop, a mechanism possibly implicated in peripheral sensitization[90], and those with chronic cluster headache may become desensitized, resulting in lower plasma CGRP levels secondary to depletion of CGRP from trigeminal afferents[89]. A mechanism similar to that of capsaicin-induced desensitization where repeated capsaicin applications to the nasal mucosa have resulted in desensitization and time-dependent recovery of responses[91]; similar results have also been seen with the intradermal application of capsaicin which shows a steady rise of CGRP levels in the first

sampling period, but not in the second[92]. This phenomenon is thought to be attributed to the depletion of neuropeptide release from sensory afferents or decreased activity of TRPV1 channels[93,94].

Monoclonal antibody therapy in cluster headache

Galcanezumab

Galcanezumab is a humanized monoclonal antibody that antagonizes the CGRP molecule directly[95]. It has been investigated for the prophylaxis of both episodic[47] and chronic[48] cluster headache in phase III, double-blinded, randomized clinical trials. It has been approved by the FDA for preventive therapy of episodic cluster headache in the United States[21].

Controlled trials

Of the 106 enrolled patients with episodic cluster headache, 49 were randomly assigned to receive galcanezumab and 57 to receive placebo[47]. The patient population was predominantly male (83%), white (85%) with a mean age of 47 years in the galcanezumab group and 45 years in the placebo group[47]. Between week 1-3, the mean percentage reduction from baseline in the weekly frequency of cluster headache attacks was 52% in the galcanezumab group compared to that of the placebo group, which was 27%[47]. In addition, 71% of patients treated with galcanezumab reported headache reduction of at least 50% in the weekly frequency of cluster headache attack at week three, as compared with 53% in the placebo group (P=0.046)[47]. From week 4-8, the mean changes in the weekly frequency of cluster headache attacks in the galcanezumab and placebo group coincided[47], suggesting that spontaneous improvement or remission of the cluster headache bout may have occurred during the second half of the double-blind phase[96,97]. No deaths or serious adverse events occurred throughout the trial. It was reported that there was a higher frequency of adverse events in the galcanezumab group compared to the placebo group (43% vs 33%), with injection-site pain occurring most commonly (8%; 4/49)[47]. Discontinuation secondary to adverse events occurred in 4% of the patients in the galcanezumab group and 2% of those in the placebo group[47]. The clinical trial concluded that galcanezumab at a dose of 300mg once monthly was effective in the prophylaxis of episodic cluster headache, with CGRP playing a substantial role in the pathophysiology of cluster headache[47,83]. Remarkably, in a correlation of Patient Global Impression of Improvement data from the study, a rating of "much better" or higher was seen in participants with a 43% or more reduction in attacks[98]. This data suggests that the 50% responder rates have considerable alignment with the patient's assessment of benefit. Interestingly, the true site of action of galcanezumab remains unknown, and it is widely considered that a peripheral site, such as the trigeminal ganglion[99], is responsible. Notably few IgG molecules enter the cerebrospinal fluid with a CSF to plasma concentration of 0.1%[100]. In contrast, the brain entry is somewhat greater in the hypothalamic region[101]. Moreover, fremanezumab, which partitions at about 1:1000 into the brain, has the effect of sequestering CGRP in the CSF in humans[102], which suggests the actions are more complex than widely considered.

The chronic cluster headache phase III, randomized, placebo-controlled study

investigating galcanezumab in the preventive treatment of chronic cluster headache was negative. It included 237 patients, who were randomly assigned to the placebo group (n = 120) and the galcanezumab group (n = 117)[48]. Of the participants, 73% were male, 84% identified as white, and the mean age within the galcanezumab group was 45.6 years, compared to that of the placebo group which was 44.4 years[48]. Preventive medications were allowed in the chronic cluster headache trial, in contrast to the episodic cluster headache trial, with 63% of patients using at least one preventive medication and 49.8% of all patients using verapamil, although this did not show treatment interaction in later subgroup analysis[48]. Unlike the episodic cluster headache trial, the primary endpoint was not met, with the mean reduction in weekly cluster headache attack frequency reported as 5.4 attacks in the galcanezumab group, compared to 4.6 attacks in the placebo group across 12 weeks (P = 0.334) (48). Whilst not seen at any other biweekly interval, a significant decrease in weekly attack frequency with galcanezumab compared to placebo was observed between weeks 1-2 (−4.0 attacks vs −1.8 attacks, respectively; P=0.006)[48]. Similarly, the secondary endpoints of the trial were not achieved. There was no difference observed between the mean percentage of patients with at least a 50% reduction in weekly attack frequency from baseline across weeks 1 to 12 (27.1% placebo; 32.6% galcanezumab; P = 0.170) and a similar percentage of patients in each treatment group met the definition of sustained response, defined as at least a 50% reduction in the weekly cluster attack frequency from baseline to weeks 3-4 and maintained up to week 12 (17.5% placebo; 16.2% galcanezumab; P=0.946)[48]. No deaths were reported throughout the trial. Five serious adverse events were reported, with three occurring in the placebo group (melaena, non-cardiac chest pain, depression), whilst two occurred in the galcanezumab group (atrial fibrillation [discontinued treatment] and constipation [deemed treatment related, however resulted in no changes to study treatment], all of which were marked as resolved. The galcanezumab group were more likely to report adverse events (62.5% placebo; 71.8% galcanezumab), with injection site pain, nasopharyngitis, injection site erythema, and nausea were reported by at least 5% of galcanezumab-treated patients. The majority of patients (92.5%) reporting treatment-emergent adverse events as mild or moderate. Only two patients, one in the placebo group and one in the galcanezumab group, discontinued the trial secondary to adverse events. The lack of efficacy of galcanezumab for the preventive management of chronic cluster headache was unexpected, however, the authors speculate that CGRP may have reduced influence in chronic cluster headache compared to that of episodic[48]. Infusions of CGRP have been shown to induce less attacks in patients with chronic cluster headache (50%), compared to that of episodic (89%)[20], and CGRP levels are demonstrably lower in patients with chronic cluster headache (65.9 ± 30.5 pmol/L) compared to those with active episodic cluster headache (89.7 ± 26.9 pmol/L)[89]. Moreover, it is conceivable that chronic cluster headache may be more treatment-resistant than episodic[48], with a subset of patients refractory to preventive treatments[33,103, 104] and higher reports of suicidal ideation and behaviour, suggesting a more severely affected patient population[48].

Real world experience

Outside the realm of clinical trials, real-world experience using 240 mg of galcanezumab for the preventive treatment of episodic cluster headache has provided positive results[105]. In a sample of 47 patients, the median time from baseline to remission was reported as 17 days (IQR: 5.0 ~ 29.5), with 13 patients attack-free in one week (27.7%), 10 patients in two weeks (21.3%), 6 patients in three weeks (12.8%) and the remaining in one month[105]. The majority of patients (91.5%) received only one dose of galcanezumab[105]. Of the 33 patients with complete headache diary data, the mean number of cluster headache attacks decreased from 8.6 attacks (SD 4.8) at baseline to 1.8 attacks (SD 2.4) at week three, with 78.8% of patients reporting at least a 50% reduction in weekly cluster headache attacks and 79.3% of patients reducing their acute medication consumption by at least 50%[105]. Patients equally had a good perception of galcanezumab therapy, with 45 (95.7%) patients reporting feeling "very much better", "much better" or "a little better" measured using the PGI-I scale[105]. Galcanezumab therapy was safe and well-tolerated with no serious adverse events[105]. In patients where galcanezumab was added to conventional preventive therapy for cluster headache, the median time from baseline to remission in weekly cluster headache attacks was reported as 15.5 days (IQR: 3.8-22.1), which was notably less time than patients using galcanezumab as a first-line preventive therapy (median: 21 days, IQR: 12.0-31.5 days). In patients using galcanezumab as sole prevention, the median response time was reported as 12.5 days (IQR: 12.0-19.8)[105]. There was no difference in the effectiveness of galcanezumab at week three between patients who received galcanezumab in addition to conventional preventive therapy and patients who received initial preventive therapy with galcanezumab. (83.3%, vs 66.7%, $P = 0.36$)[105].

Fremanezumab

Fremanezumab is a humanised monoclonal antibody designed to bind to and prevent the CGRP ligand interaction with its receptor[106].

Controlled trials

It was originally trialed as a preventive for both episodic and chronic cluster headache in the ENFORCE phase III development programme, however, this was later terminated as a result of likely failure to meet the primary endpoints of a mean change in the weekly average number of cluster headache attacks from baseline during the 4-week treatment duration of the trial[107]. In the episodic cluster headache prevention study[49], varying doses of fremanezumab were compared against a placebo. In 169 cases, there were no differences in the weekly average number of cluster headache attacks between the arms during the four-week period (fremanezumab high-dose arm: 7.6 attacks vs. fremanezumab low-dose arm: 5.8 attacks vs. placebo arm: 5.7 attacks). Whilst similarly, in the chronic cluster headache trial involving 254 cases (NCT02964338), there were no differences in the weekly average number of cluster headache attacks between the arms during the four-week period (fremanezumab high-dose arm: 15.5 attacks vs. fremanezumab low-dose arm: 8.7 attacks vs. placebo arm: 12.2 attacks). The long-term safety and efficacy study was additionally terminated (NCT03107052). Interestingly, the endpoint in both fremanezumab trials was at four weeks, whilst the endpoint in the galcanezumab episodic

cluster headache trial[47] was at three weeks, which may have produced a negative result given the possibility of early spontaneous remission owing to the natural course of cluster headache.

Real world experience

Despite futile results in clinical trials, a recent case series by Kashiwagi et al. demonstrated positive clinical experience using fremanezumab, administered quarterly, in patients with migraine and comorbid cluster headache[108]. Of the two patients who used fremanezumab, both reported large reductions in cluster headache attack frequency, from 34 to 2 attacks and 23 to 3 attacks respectively, in addition to reduced pain intensity with both reporting their pain had decreased by 8 points (10-2) on the numerical rating scale[108].

Erenumab

Erenumab is a humanised monoclonal antibody against the CGRP receptor complex, originally developed for the prophylaxis of migraine[109].

Controlled trials

Erenumab has recently been assessed for effectiveness as a preventive treatment in patients with chronic cluster headache (NCT04970355) using a loading dose of 280 mg followed by 140 mg for 4 weeks. The CHERUB01 study was conducted in a randomized, double-blind, parallel- group, placebo-controlled design over two arms across ten weeks. The trial completed on September 27, 2023 and the results are still to be published.

Real world experience

Real-world evidence on the use of erenumab exists in the form of case series and reports. One case report outlines the successful response of 70 mg of subcutaneous erenumab as a preventive treatment in a 38-year-old female patient with a primary diagnosis of chronic cluster headache and comorbid migraine[110]. She had previously failed verapamil, topiramate, lithium, melatonin, sodium valproate and non-invasive vagus nerve stimulation[110]. Following a single administration of erenumab, the patient's cluster headache attacks dramatically reduced from a baseline of three attacks daily to nine attacks over the course of one month[110]. Erenumab was well-tolerated with no reported adverse effects[110]. A larger case-series of five patients both with migraine and cluster headache similarly reported positive results on cluster headache attack frequency and intensity alongside migraine[111]. The case-series involved a mixture of patients with chronic (n=4) and episodic cluster headache (n=1), with all patients experiencing at least 1 attack per day for a minimum of 45 minutes[111]. Patients included within the series had failed at least three previous preventives, with one patient having failed a total of six preventives[111]. Following the administration of erenumab, all patients reported a reduction in cluster headache attack frequency and severity[111]. One patient with episodic cluster headache reported significant improvement after the second administration of 140mg erenumab with decreased migraine attacks (7 to 3 migraine attacks per month) and cluster headache attack frequency (46 to 23 attacks per month), of which remitted after the fourth administration of erenumab[111]. Whilst those with chronic cluster headache noticed significant improvement in cluster headache attack frequency from the second to the third administration of erenumab, with complete remission occurring from the third to the sixth administration of erenumab[111].

Eptinezumab

Intravenous eptinezumab[112] is currently being investigated to evaluate its efficacy in patients with episodic cluster headache in a randomized, double-blind, placebo-controlled study (ALLEVIATE) across a study period of 12 weeks, with an additional 8-week safety follow- up period. The trial completed on the 29th June, 2023, however, no results have been posted as of writing (NCT04688775). In similar fashion, the long-term safety and tolerability of eptinezumab in patients with chronic cluster headache was also investigated (CHRONICLE; NCT05064397) in an interventional, open-label, fixed-dose multiple administration study over the course of one year. The trial completed on the 10th May 2023 and the results are not published as of writing. No real-world experience reporting the role of eptinezumab for the prophylaxis of cluster headache was found whilst writing this review.

Future perspectives

The evidence for using CGRP monoclonal antibody treatments as a preventive treatment so far has produced mixed results, with positive results seen in real-world studies[105,108, 110,111], moderate effects observed in clinical trials for episodic cluster headache[47] and little-to-no response seen in clinical trials for chronic cluster headache patients[48,107], summarized in Table 1. This may be attributed to early spontaneous remission owing to the natural course of the disease[47] or equally, the relatively high rates of placebo effect, which make it difficult to prove the efficacy of a new therapy[21]. Considering the stark difference in results observed between episodic and chronic cluster headache, it is plausible that CGRP sensitivity and its influence may be different amongst the subtypes of cluster headache. This has been previously acknowledged by studies documenting reduced CGRP serum levels in chronic cluster headache[89], and CGRP's reduced ability to induce attacks in those with chronic cluster headache[20]. It may possibly occur as a result of desensitization to CGRP in chronic cluster headache[89]. Moreover, given that CGRP serum levels normalize when patients are out-of-bout, it has been suggested that CGRP monoclonal antibodies may only be effective in active phases of the disorder[20] and perhaps, anti-CGRP therapy should be considered as a cluster headache modifying treatment, rather than a preventive treatment, which may be used interrupt the development of a new active phase or prevent chronification[11]. Additionally, it is still important to consider a possible direct central mechanism of CGRP signalling in cluster headache which may facilitate central pain sensitization. IgG antibodies have been shown to enter the cerebrospinal fluid in a ratio of 1:100 compared to plasma[100,102]. Moreover, other IgGs have been shown to have considerable inter-individual CSF to plasma ratios[113]. Perhaps there is a more pharmacokinetic explanation that might explain some of the variance reported. Outside of physiological differences, it is possible that study designs and treatment protocols may have to be adjusted in chronic cluster headache patients to visualise the effects of monoclonal antibodies, such as changing the treatment intervals, doses or durations[11], with the intention to account for the differences seen between episodic and chronic cluster headache, such as treatment-resistance and severity of the disease[33,103].

Table 1. Synopsis of the controlled and open-label clinical trials for the treatment of cluster headache with CGRP monoclonal antibodies. Note that trials without results posted have not been included. (Abbreviations: PBO – placebo, GZB: galcanezumab, CH: cluster headache).

Monoclonal antibody Study	Total *n*	Dose	Placebo	Key primary endpoints	Key secondary endpoints	Key finding
Episodic CH						
Galcanezumab Controlled trial (Goadsby et al. New Engl J Med 2019;381(2):132-41.)	106	300mg once monthly	Yes	Mean (±SE) reduction in the weekly frequency of CH attacks (week 1-3): GZB -8.7 ±1.4 PBO -5.2 ±1.3	Reduction of ≥ 50% in the weekly frequency of CH attacks at week 3: GZB 71% vs PBO 53% (*P* = 0.046)	
Galcanezumab Open-label study (Mo et al. J Headache Pain. 2022;23(1):132.)	50	Two 120mg doses	No			Reduction of ≥ 50% in the weekly frequency of CH attacks at week 3 (*n*=33): 78.8% of patients
Fremanezumab Controlled trial (Lipton et al. Cephalalgia. 2019;39(1S):358-9.) NCT02964338. STUDY TERMINATED.	169	675/225/225 mg (LD) and 900/225/225 mg (HD) at week 0, 4 and 8.	Yes	Mean (±SE) reduction in the weekly frequency of CH attacks (week 1-4): LD -5.8±1.02, HD -7.6 ±1.01, PBO -5.7 ±1.00	Reduction of ≥ 50% in the weekly frequency of CH attacks at week 4: LD 55% vs HD 75% vs PBO 60%	
Chronic CH						
Galcanezumab Controlled trial (Dodick et al. Cephalalgia. 2020;40(9):935-48.)	237	300mg once monthly	Yes	Mean (±SE) reduction in the weekly frequency of CH attacks (week 1-12): GZB -5.4 vs placebo -4.6 (*P* = 0.334)	Reduction of ≥ 50% in the weekly frequency of CH attacks (week 1-12): GZB 32.6% vs PBO 27.1% (*P* = 0.170)	
Fremanezumab Controlled trial NCT02964338. STUDY TERMINATED.	259	675/225/225 mg (LD) and 900/225/225 mg (HD) at week 0, 4 and 8.	Yes	Mean (±SE) reduction in the monthly average number of CH attacks up to week 12: PBO -12.2±2.32, LD -8.7±2.26, HD -15.5±2.24	Reduction of ≥ 50% in the weekly frequency of CH attacks (week 1-12): LD 40% vs HD 45% vs PBO 40%	
Erenumab Case report (Riederer et al. Cephalalgia Reports. 2020;3.)	1	X4 doses of 70mg over 25 weeks	No			CH attack frequency decreased from baseline of 3 attacks/day to several attacks per week.
Mixed cohort						
Fremanezumab Controlled trial ENFORCE: NCT03107052. STUDY TERMINATED.	275	225 mg monthly (D1), 675/225 mg monthly	No	Number of adverse events (week 0-68): D1 60.4% vs D2 51.7% vs D3 59.2%	Number of clinically significant abnormal laboratory results (week 0-68): D1 1.6% vs D2 0.0% vs D3 1.5%	

		(D2), 675 mg quarterly (D3)				
Erenumab Case-series (Silvestro et al. Headache. 2020;60(6):1187-95.)	5 (1 eCH, 4 cCH)	Monthly doses of 70 or 140 mg	No			eCH: Reduced CH attacks from second administration and complete resolution until the eighth administration. cCH: Reduced CH attacks from second administration and complete resolution until the sixth administration.

Conclusion

Calcitonin gene-related peptide is a potent vasodilator and important neurotransmitter/ neuromodulator found in both the central and peripheral nervous systems and plays a substantial role in primary headache disorders. It is clear that calcitonin gene-related peptide is involved in cluster headache pathophysiology, however, its full extent of action and influence amongst episodic and chronic phenotypes of cluster headache is still to be discovered. Out of the four monoclonal antibodies that target calcitonin gene-related peptide or its receptor, galcanezumab has been reported as effective and well-tolerated in a randomized, placebo-controlled phase III trial for the preventive treatment of episodic cluster headache. More research is required to understand fully the effects of calcitonin gene-related peptide and its influence in both episodic and chronic cluster headache in order to deliver more effective preventive treatment options for this very disabling disorder.

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RW has no disclosures

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