Case Report

Fremanezumab and Non-High-Dose Galcanezumab for Comorbid Cluster Headache in Patients With Migraine: 3 Cases

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Fremanezumab and Non-High-Dose Galcanezumab for Comorbid Cluster Headache in Patients with Migraine: 3 Cases

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Abstract: A new treatment option for cluster headache (CH) prevention is needed. Monoclonal antibodies (mABs) against calcitonin gene-related peptide (CGRP) ligands are used as a preventative treatment for migraine. Considering the CGRP's role in the CH attack's ignition and upkeep, fremanezumab and galcanezumab have been evaluated for CH preventative treatment. However, only high-dose (300 mg) galcanezumab was proven for episodic CH prevention. We herein report 3 cases of migraine and comorbid CH with previous failures of preventive treatments. The 2 cases were treated with fremanezumab and the one with non-high-dose galcanezumab. All 3 cases showed good results not only on migraine but also on CH attacks. Our report suggested the efficacy of CGRP-mABs for CH prevention. Our cases differed from the cases in the [phase 3 trials of CGRP-mABs for CH prevention in the following 2 points. First, the patients had both migraine and comorbid CH. Second, the combined use of CGRP-mABs with preventative drugs for CH, such as verapamil and/or prednisolone, was performed. Future accumulation of real-world data may prove the efficacy of CGRP-mABs for CH prevention.

Keywords: anti-calcitonin gene-related peptide monoclonal antibodies; cluster headache; migraine; real-world; galcanezumab; fremanezumab; comorbidity

1. Introduction

Cluster headache (CH) is one of the primary headache disorders. CH attacks are characterized by excruciating unilateral headache or facial pain accompanied by ipsilateral autonomic symptoms and restlessness or agitation [1]. CH interferes with quality of life due to its severe pain attacks. A first-choice preventative drug for CH during cluster periods is verapamil in Japan, according to the Clinical Practice Guideline for Headache Disorders 2021. If it is ineffective, contraindicated, or discontinued due to side effects, the choice of preventative treatment will be difficult.

Monoclonal antibodies (mABs) against calcitonin gene-related peptide (CGRP) ligands are used as a preventative treatment for migraine [2–4]. CGRP-mABs are now widely used as epidemiological studies [5–7] are conducted, and patient interest in treatment increases [8]. Considering the CGRP's role in the CH attack's ignition and upkeep [9], fremanezumab and galcanezumab have been evaluated for CH preventative treatment. However, only high-dose (300 mg) galcanezumab was proven for episodic CH prevention, but fremanezumab and non-high-dose galcanezumab have not been proven effective for CH prevention [10].

We herein report 3 cases of migraines without aura and comorbid CH successfully treated by fremanezumab or non-high-dose galcanezumab for both migraine attack and CH attack prevention. We aimed to treat the migraine and consequently treated the cluster headache as well. Our report suggests that they may be preventative treatments in patients with migraine and comorbid CH. This article was previously posted to the Researchgate preprint server in December 2022. All the patients provided written informed consent.

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2. Case presentation

The patients' therapeutic effects are summarized in Figures 1 and 2.

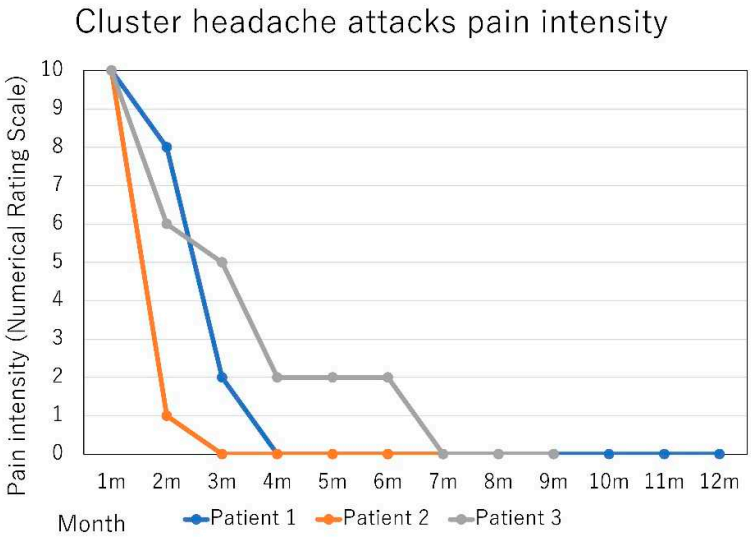

Figure 1. Change in the frequency of cluster headache (CH) attacks in the course of treatment.

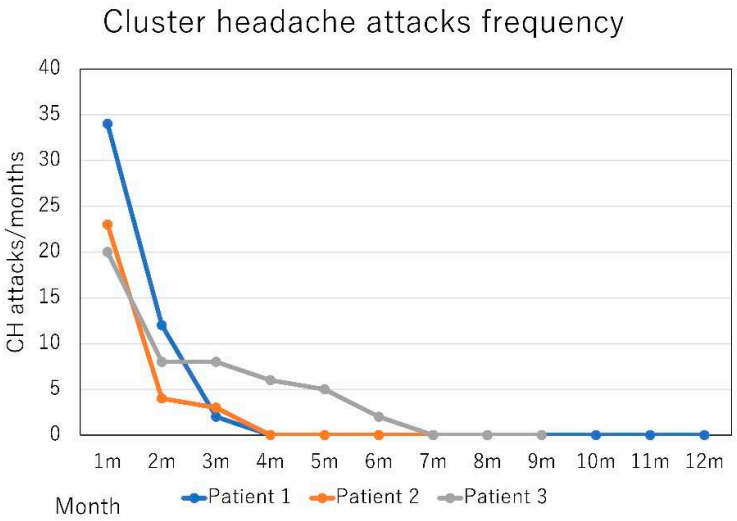

Figure 2. Change in the intensity of cluster headache attacks in the course of treatment.

Patient 1: A 35-year-old man presented with 15 years history of excruciating, stabbing headache episodes with right orbital-periorbital localization, associated with ipsilateral autonomic symptoms such as ptosis, rhinorrhea, eyelid edema, and agitation. The attacks ranged from 2 to 5 per day and lasted 40-60 minutes, treated with a sumatriptan injection of 3 mg/0.5 mL. These attacks did not express in the period of remission, and the about 3-week cluster periods occurred 2-3 times per year. Verapamil 120 mg did not have effect for CH prevention. He also reported migraine episodes 5 times per month, resolved after over-the-counter combination analgesics use. The headaches were with moderate intensity, aggravation by routine physical activity, associated with photophobia, phonophobia, and nausea, lasting 4-8 hours. The headaches are located at the center of his forehead. Previously, he had started to take amitriptyline 20 mg as a prophylactic treatment but stopped due to drowsiness. Based on the diagnosis of episodic CH (International Classification of Headache Disorders 3rd edition (ICHD-3) code 3.1.1) and migraine without aura (code 1.1), fremanezumab 675

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mg was administered quarterly to prevent migraine attacks. After 3 months, monthly headache days (MHD) and monthly acute medication intake days (AMD) improved from 5 to 3 and 5 to 1, respectively. The frequency and pain intensity of CH attacks also improved from 34 to 2 and the numerical rating scale (NRS) from 10 to 2, respectively. The patient reported sustained response until the 12 months (5-time administration of 675 mg fremanezumab), the time of follow-up appointment, and continued fremanezumab use. There has been no side effects of fremanezumab.

Patient 2: A 37-year-old man presented with 12 years history of excruciating, stabbing headache episodes with left orbital-periorbital localization, associated with ipsilateral autonomic symptoms such as rhinorrhea, forehead sweating, and agitation. He had had a suicide attempt. The attacks ranged from 2 to 4 per day and lasted 120-180 minutes, treated with a sumatriptan 50 mg intake. These attacks did not express in the period of remission, and the about 2-week cluster periods occurred 1-2 times per year. Verapamil 240 mg and prednisolone 40 mg did not have effects as CH prevention. He also reported migraine episodes 5 times per month, resolved after sumatriptan 50 mg intake or over-the-counter combination analgesics use. The headaches were with bilateral temporal localization, moderate-severe intensity, aggravation by routine physical activity, and associated with nausea, lasting 4 hours. Previously, he had started to take valproic acid 200 mg as a prophylactic treatment but stopped due to drowsiness. Based on the diagnosis of episodic CH (code 3.1.1) and migraine without aura (code 1.1), fremanezumab 675 mg was administered quarterly to prevent migraine attacks. After 3 months, MHD and monthly AMD improved from 5 to 0 and 5 to 0, respectively. The frequency and pain intensity of CH attacks also improved from 23 to 3 and NRS from 10 to 2, respectively. The patient reported sustained response until the 7 months (3-time administration of 675 mg fremanezumab), the time of follow-up appointment, and continued fremanezumab use. There has been no side effects of fremanezumab.

Patient 3: A 59-year-old man presented with a 12-year history of severe, stabbing headache episodes that were localized to the left orbit and the periorbit and were accompanied by ipsilateral autonomic symptoms such as rhinorrhea, forehead perspiration, eyelid edema, and psychomotor agitation. He had made a suicide attempt on his life. Attacks ranged from 2 to 4 per day and lasted 180 minutes. Sumatriptan 50 mg or a 3 mg/0.5 mL injection was used to treat them. They did not, however, exhibit strong therapeutic responses. For the previous five years, there had been no remission times. Prednisolone 40 mg and verapamil 240 mg had no impact on CH prophylaxis. He also stated that he experienced migraines four times each month. He took sumatriptan 50 mg or a combination of over-the-counter painkillers. The headaches were severe, localized to the left temporal region, aggravated by normal physical activity, and lasted for eight hours. They were also accompanied by photophobia, phonophobia, and nausea. He had previously taken 400 mg of valproic acid as a preventative measure, but he discontinued it due to skin rash and sleepiness. Galcanezumab was used to stop migraine attacks based on the diagnoses of migraine without aura (code 1.1) and chronic CH (code 3.1.2). Galcanezumab 120 mg was administered subcutaneously once per month after a 240 mg loading dose. MHD and AMD both improved from 4 to 2 and 10 to 2, respectively, after three months. The frequency of CH episodes decreased from 20 to 8, and the pain level decreased from 10 to 5, respectively. At seven months, chronic CH had entered remission. The patient reported ongoing use of galcanezumab, a sustained response that lasted for ten months, at the time of the follow-up session. There have been no side effects of galcanezumab.

3. Discussion

The 2 keys of CH pathophysiology are the hypothalamus as the central structure and generator of CH and the trigeminal nerve as the peripheral structure for pain and autonomic symptoms. CH's circadian and circannual clustering of attacks may suggest a relationship with the endogenous biological clock. The hypothalamus is responsible for circadian rhythm, and neuroimaging studies have shown functional and structural alternations of the hypothalamus in CH patients [11]. As for the mechanism by which trigeminal overexcitation causes pain and parasympathetic activation, it is thought that the trigeminal nerve activity is heightened, and this excitement extends to the superior salivary nucleus, resulting in excitation of parasympathetic nerves from the pterygopalatine ganglion

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to the large intracranial vessels, lacrimal gland, and nasal mucosa. A series of autonomic symptoms, such as running tears and nasal discharge, are produced. Furthermore, the increased release of CGRP and other substances upon stimulation of the trigeminal ganglion and the increase in CGRP in jugular venous blood during CH attacks suggest a close involvement of the trigeminal nerve and CGRP in CH [10]. Hypothalamus, trigeminal nerve, and CGRP are closely involved in both migraine and CH. Migraine and CH may also be accompanied by clinically overlapping findings; up to 46% of CH patients can show migraine-like features, and migraine patients can have typical trigeminal autonomic symptoms [12]. Also, 15.6% of CH patients have comorbid migraine, although comorbid CH in migraine cohorts has yet to be investigated [13]. Taken together, CGRP functional blockade may alleviate neurogenic inflammation and may reduce pain pathway sensitization, in both migraine and CH.

Fremanezumab is effective in preventing episodic and chronic migraine. In the episodic CH prevention study (NCT02945046), fremanezumab dosages of 900/225/225 mg for the high-dose arm, 675 mg/placebo/placebo for the low-dose arm, and placebo arm were compared. The dosing schedule was 0/4/8 weeks. Of the 169 cases, during the 4-week period, there were no differences in the weekly average number of CH attacks between the arms (fremanezumab high dose: -7.6 attacks/week vs. fremanezumab low dose: -5.8 attacks/week vs. placebo: -5.7 attacks/week).

Galcanezumab is used for the prevention of episodic and chronic migraine. One phase 3 randomized placebo-controlled trial (NCT02397473, CGAL study) investigated the efficacy of galcanezumab (subcutaneous injection of 300 mg/month for two months) for episodic CH prevention. Of the 106 cases, galcanezumab effectively reduced CH attack frequency across week 1 to week 3 (galcanezumab: - 8.7 attacks/week vs. placebo: - 5.2 attacks/week, $p = 0.036$). There are no studies on the use of non-300-mg galcanezumab for CH prevention.

Study design for episodic CH preventative therapy is difficult in the following points. Spontaneous remission of CH can occur. Irregularity and changes of the onset and duration of cluster period also exist. Therefore, these negative study results on CGRP-mABs for episodic CH are not absolute. They could be meaningful if the study design and cases are rigorously examined. Also, our case is different from the cases in the phase 3 trials in the following 2 points; First, the patients had both migraine and comorbid CH. Second, the combined use of CGRP-mABs and preventative drugs for CH, such as verapamil and/or prednisolone, were performed. It is hoped that the future accumulation of real-world data may prove the efficacy of CGRP-mABs for CH, for which treatment options are scarce.

4. Conclusions

We herein report 3 cases of migraines without aura and comorbid CH successfully treated by fremanezumab or non-high-dose galcanezumab for CH attack prevention. We aimed to treat the migraine and consequently treated the cluster headache as well. Our report suggests that they may be preventative treatments in patients with migraine and comorbid CH. However, the issue of the possibility arose that the CH cycle spontaneously resolved and was not a result of the medication, especially in the first two cases. Further investigation of CGRP-mABs for migraine and CH prevention is needed.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Itoigawa General Hospital Ethics Committee (Approval number; 2022-4).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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