Erenumab for chronic cluster headache: A case report

Franz Riederer1,2 and Allyson M Wenner3

Abstract
The preventive treatment for cluster headache is often limited by a lack of efficacy or side effects. Calcitonin gene-related peptide (CGRP) has been implicated in the pathophysiology of cluster headache. Galcanezumab, a monoclonal antibody against calcitonin gene-related peptide (CGRP), significantly reduced the frequency of episodic cluster headache attacks. We report the case of a 38-year-old woman with chronic refractory cluster headache and comorbid migraine who received erenumab in 4 repeated doses of 70 mg subcutaneously over 25 weeks. Attack frequency decreased from three attacks per day to several attacks per week. Erenumab seemed to be highly effective in the prevention of cluster headache attacks in this patient. We suggest that randomized control trials should be performed.

Keywords
case report, cluster headache, chronic, CGRP, erenumab, monoclonal antibody, refractory

Introduction
Cluster headache is an extremely severe primary headache condition associated with significant suffering and burden that has still limited treatment options. Cluster headache attacks last between 15 min and 180 min and can occur up to 8 times/day, accompanied by autonomic symptoms and/or agitation.1 Preventive treatment is often limited due to side effects or lack of effectiveness, particularly in patients with chronic cluster headache. While oral steroids are only recommended for short-term use, verapamil and lithium can be used for long-term prophylaxis but require careful monitoring.2,3 Verapamil has the potential side effects of ankle edema and gingival hyperplasia and requires electrocardiograms before initiation of the therapy, during dose titration, and even on stable doses because cardiac rhythm abnormalities can develop.2,3 Lithium has limited evidence for efficacy in cluster headache and may cause tremor, while long-term use can provoke kidney dysfunction and hypothyroidism.4

Since calcitonin gene-related peptide (CGRP) is believed to be involved in the pathophysiological development of cluster headache5 and monoclonal antibodies against CGRP or the CGRP-receptor are effective in preventing migraine with few side effects, several trials investigating CGRP antagonists for the preventive treatment of cluster headache have been conducted. Galcanezumab (300 mg) has been shown to significantly reduce the occurrence of cluster headache attacks during the first 3 weeks in patients being treated for episodic cluster headache.6 However, similar trials in chronic cluster headache (fremanezumab and galcanezumab) and another trial in episodic cluster headache (fremanezumab) did not reach the primary endpoints or were halted.7–9 We present a patient with chronic cluster headache who responded to treatment with erenumab, a monoclonal antibody against the CGRP

1 Department of Neurology, Clinic Hietzing with Neurological Center Rosenhuetegel and Karl Landsteiner Institute for Clinical Epilepsy Research and Cognitive Neurology, Vienna, Austria
2 Faculty of Medicine, University of Zurich, Switzerland
3 Medical University of Vienna, Austria

Corresponding author:
Franz Riederer, Department of Neurology, Clinic Hietzing with Neurological Center Rosenhuetegel and Karl Landsteiner Institute for Clinical Epilepsy Research and Cognitive Neurology, Riedelgasse 5, A-1130 Vienna, Austria.
Email: franz.riederer@uzh.ch
receptor that had been developed for migraine prevention. Until now there is only one case series showing that erenumab could be effective in cluster headache. The patient was informed of the off-label use of erenumab and gave her written informed consent to the publication of her medical history in anonymized form. Ethics approval was not necessary. The patient kept a headache diary and was followed up by telephone or visits every 2–4 weeks.

Case report

A 38-year-old woman suffered from cluster headache attacks since age 18 and also from occasional migraine without aura attacks. Her typical cluster attacks followed a circadian pattern and were strictly right-sided in periorbital and temporal regions and would last between 1 h and 2 h, associated with ipsilateral ptosis, lacrimation, facial sweating, and the subjective feeling of needing to move. These attacks of “extreme” intensity responded to subcutaneous injection of sumatriptan 6 mg or nasal injection of zolmitriptan 6 mg, whereas therapy with 100% oxygen at a high flow rate of 7–12 l/min led to minimal improvement. The attacks could be suppressed completely by oral steroids or through occipital infiltration of the greater occipital nerve with a mixture of betamethasone and xylocaine. Migraine attacks were mostly unilateral, less severe than her cluster headache attacks, slower in onset lasting for several hours and were associated with motion intolerance and nausea. An MRI scan of the brain was normal. Sixteen years after the initial onset, her cluster headaches became chronic and she experienced only a few attack-free weeks per year. Preventive treatments, including verapamil, topiramate, lithium, melatonin, and valproate or noninvasive vagus nerve stimulation, were limited by their side effects or lack of efficacy. A series of ketamine infusions led to a 2-week attack-free period. The patient was taking 240 mg/day of verapamil, 5 mg/day of melatonin, and 150 mg/day of trazodone when she was suffering from 3 cluster attacks per day. She received a single injection of 70 mg of erenumab subcutaneously and reported only 9 attacks over the following 4 weeks. As shown in Figure 1, repeated application of erenumab had a reproducible effect on cluster attack frequency over 25 weeks, with only a few attacks per week after injection. The patient had 1 migraine day after the first injection and 3 migraine days after the second, after the third injection, no migraine attacks were reported. The patient reported no side effects.

Discussion

The presented case shows that erenumab, a fully human monoclonal antibody against the CGRP receptor complex that has been developed for preventing migraine, could also be effective for the preventative treatment in chronic cluster headache. The patient also suffered from migraine without aura; however, the primary complaint was cluster headache attacks.

In this patient, erenumab seemed to be highly effective for the preventive treatment. As this a single case study, placebo effect or spontaneous improvement cannot be ruled

Figure 1. Decrease of attack frequency in a patient with chronic cluster headache following treatment with erenumab. The time point of treatment with erenumab 70 mg subcutaneously is indicated with a brown triangle.
out completely. However, this was considered unlikely since a reproducible effect was seen after each injection and attack frequency increased before the next dose. Furthermore, the patient had not responded to multiple treatments in the past. It could be assumed that an even better response might have been achieved with a higher dose, for example, 140 mg erenumab every 4 weeks.

Very recently, during the final editing of this article, another case series of five patients with chronic or episodic cluster headache and comorbid migraine was published. The authors reported a decrease in frequency and intensity of cluster headache attacks after treatment with monthly 140 mg erenumab.

Considering that cluster headache is a very severe headache condition with treatment options often limited by lack of efficacy or side effects, there is a clear need for new therapeutic approaches. The pathophysiology of cluster headache involves the a synchronized abnormal activity of the hypothalamus, trigeminovascular system, and the autonomic nervous system. CGRP levels are elevated during spontaneous cluster headache attacks, and CGRP has been shown to evoke attack onset during the active phases of episodic cluster headache and—although less frequently—in patients with chronic cluster headache. CGRP is a vasodilatory pro-inflammatory signaling molecule that is abundant both centrally and peripherally in the trigeminovascular system. CGRP blockade decreases neurogenic inflammation and sensitization in pain pathways. Galcanezumab, a humanized monoclonal antibody against CGRP that was developed for preventing migraines, is also effective in patients with episodic cluster headache and has been approved by the FDA for this indication. High-dose fremanezumab has been shown to numerically decrease the amount of cluster headache attacks in the first 4 weeks after application more than placebo in patients with episodic cluster headache; however, the primary endpoint (reduction of weekly cluster headache) throughout weeks 1–4) of this study was not reached. As CGRP induces cluster headache attacks in chronic cluster headache less frequently than in the episodic form and trials with CGRP antibodies were negative in chronic cluster headache, it could be considered that the role of CGRP in chronic cluster headache is less important. It could also be speculated that certain cluster headache phenotypes responsive to antagonists of CGRP or its receptor will be identified in the future. There are currently no data from controlled trials, whether antagonists against the CGRP-receptor complex (erenumab) could be particularly effective for the prevention of cluster headache.

Conclusions

Erenumab may be effective in the prevention of cluster headache with comorbid migraine. We suggest that erenumab should be investigated for the prevention of cluster headaches in controlled trials, especially considering its favorable tolerability.

Clinical implications

- Erenumab could be effective for the prevention of cluster headache with comorbid migraine.
- Randomized controlled trials should be conducted.
- Off-label use of erenumab for chronic cluster headache with comorbid migraine could be considered.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FR served as a consultant for Novartis, Eli Lilly, and Teva and also has received speaker honoraria from Novartis, Teva, Menarini, and Burgerstein Foundation.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Franz Riederer https://orcid.org/0000-0002-9722-9754

References

1. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia 2018; 38: 1–211.
2. Villar-Martinez MD, Chan C, and Goadsby PJ. Evolving options for the treatment of cluster headache. Curr Opin Neurol 2020; 33: 323–328.
3. Cohen AS, Matharu MS, and Goadsby PJ. Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy. Neurology 2007; 69: 668–675.
4. Brandt RB, Doesborg PGG, Haan J, et al. Pharmacotherapy for Cluster Headache. CNS drugs 2020; 34: 171–184.
5. Giani L, Proietti Cecchini A, and Leone M. Anti-CGRP in cluster headache therapy. Neurological Sci 2019; 40: 129–135.
6. Goadsby PJ, Dodick DW, Leone M, et al. Trial of galcanezumab in prevention of episodic cluster headache. N Engl J Med 2019; 381: 132–141.
7. Dodick DW, Goadsby PJ, Lucas C, et al. Phase 3 randomized, placebo-controlled study of galcanezumab in patients with chronic cluster headache: results from 3-month double-blind treatment. Cephalalgia 2020. Epub ahead of print 12 February 2020. DOI: 10.1177/033310242095321.
8. Lipton R, Diener HC, Barbanti P, et al. Efficacy and safety of fremanezumab for the prevention of episodic cluster headache: results of a randomized, double-blind, placebo-controlled phase 3 study. In: International Headache Conference, Dublin, 2019, Poster IHC-OR-040 2019, 5–8 September 2019, Dublin, Leinster, Ireland.
9. Yuan H, Spare NM, and Silberstein SD. Targeting CGRP for the prevention of migraine and cluster headache: a narrative review. *Headache* 2019; 59(2): 20–32.

10. Goadsby PJ, Reuter U, Hallstrom Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med* 2017; 377: 2123–2132.

11. Silvestro M, Tessitore A, Scotto di Clemente F, et al. Erenumab efficacy on comorbid cluster headache in patients with migraine: a real-world case series. *Headache* 2020; 60(6): 1187–1195.

12. Hoffmann J and May A. Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol* 2018; 17: 75–83.

13. Goadsby PJ and Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache. Neuropeptide changes and effects of acute attacks therapies. *Brain* 1994; 117(Pt 3): 427–434.

14. Vollesen ALH, Snoer A, Beske RP, et al. Effect of infusion of calcitonin gene-related peptide on cluster headache attacks: a randomized clinical trial. *JAMA Neurol* 2018; 75: 1187–1197.