Case Report

Ischemic Stroke Associated With Calcitonin Gene-Related Peptide Inhibitor Therapy for Migraine: A Case Report

Stephen Aradi, MD, Eric Kaiser, MD, PhD, and Brett Cucchiara, MD

Calcitonin gene-related peptide (CGRP) is involved in nociception and neurogenic inflammation in migraine, but also serves as a potent vasodilator acting on intracranial arteries. This latter effect raises concern about the possibility of drugs inhibiting CGRP precipitating cerebral ischemia. We describe a 41-year-old woman with migraine without aura who developed a right thalamic infarction following a first dose of erenumab, a CGRP-receptor blocker. Stroke onset occurred during a typical migraine. Imaging demonsrated right posterior cerebral artery near-occlusion initially with normalization of the vessel at follow-up imaging 2 months later, suggesting vasospasm as a possible mechanism. Extensive evaluation revealed no other specific cause of stroke or vascular risk factors aside from long-term use of oral contraceptive pills. CGRP inhibitors might be associated with ischemic stroke due to blockade of normal cerebral vasodilatory regulatory function.

Key Words: Migraine—ischemic stroke—calcitonin gene-related peptide—side effects

Background

Calcitonin gene-related peptide (CGRP) is involved in nociception and neurogenic inflammation in migraine. Erenumab, a monoclonal antibody inhibiting the CGRP receptor, has recently been introduced as a migraine preventative agent; it has a long half-life (28 days) and is dosed parenterally once monthly. As CGRP serves as a potent vasodilator acting on intracranial arteries, there is a theoretical concern that these agents might increase the risk of stroke by blocking compensatory vasodilation necessary to maintain adequate cerebral blood flow under conditions of vasoconstriction or vessel occlusion.[1] We report a case of ischemic stroke complicating treatment with the CGRP-inhibitor erenumab.

From the Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania.

Received May 31, 2019; revision received June 28, 2019; accepted July 5, 2019.

Funding: None.

Address correspondence to Brett Cucchiara, MD, Department of Neurology, University of Pennsylvania, 3 West Gates, 3400 Spruce Street, Philadelphia, PA 19104. E-mail: cucchiar@pennmedicine.upenn.edu.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.07.002

Case Report

A 41-year-old woman had episodic migraine without aura since age 32. Her migraines were managed with naproxen and sumatriptan until summer 2018, when her headache frequency increased from 4 to 8 per month. Sumatriptan was switched to rizatriptan with reduced intensity and duration of headaches, but no change in frequency. She subsequently started erenumab 70 mg; 34 days after her first dose she developed a typical migraine and took rizatriptan. Four hours later, she developed acute left hemiataxia and numbness, double vision, and dysarthria. She was diagnosed with acute ischemic stroke and given intravenous tissue plasminogen activator (tPA). Brain MRI demonstrated an acute right thalamic infarction. CT angiography of the head and neck demonstrated a proximal right posterior cerebral artery (PCA) P1 segment near occlusion, concordant with the infarct location, with a large right posterior communicating artery (Fig 1). Transesophageal echocardiography revealed no cardiac source of embolus or patent foramen ovale. Hypercoagulable testing was negative. She had been taking oral contraceptives (1-mg norethindrone/20-mcg ethinyl estradiol) for approximately 10 years; these were discontinued. She did not smoke or use illicit drugs, there was no family history of stroke or early thrombotic events, and she had no other vascular risk factors. Her symptoms

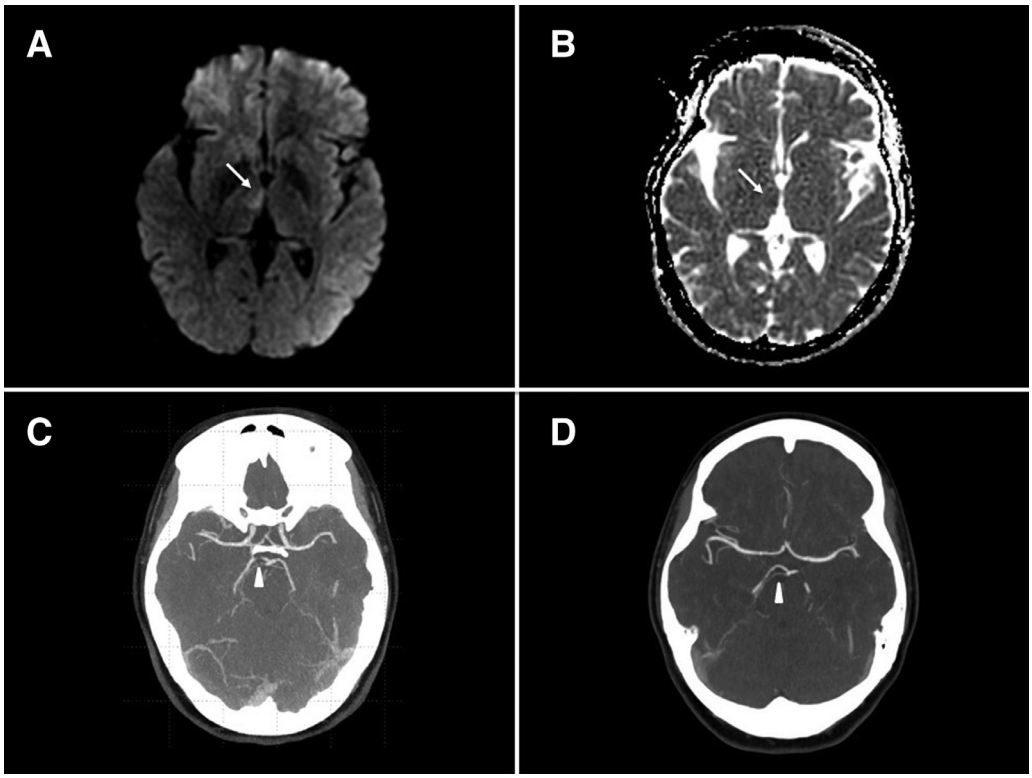

Figure 1. *MRI diffusion-weighted (A) and apparent diffusion coefficient (B) images showing acute right medial thalamic infarction (arrows). Initial computed tomography angiography (CTA) (C) shows near occlusion of the right P1 segment of the posterior cerebral artery (arrowhead) with a large right posterior communicating artery. Follow-up CTA 2 months later (D) shows normalization of the right posterior cerebral artery (arrowhead).*

improved within 12 hours following onset, with persistent mild left arm discoordination and sensory loss. She was treated with antiplatelet therapy. One week later she developed recurrent left arm clumsiness which resolved within 1-2 hours. Repeat brain MRI/MRA showed no significant change with persistent right PCA P1 near occlusion. Recurrent 30-minute episodes of left arm and leg paresthesias occurred about 3 times per week for several weeks before eventually resolving. CT angiography 2 months later showed normalization of the right P1 segment.

Discussion

Our patient suffered a posterior-circulation stroke 34 days after an initial dose of erenumab, a temporal relationship which is plausible given erenumab's long half-life. In human testing using a capsaicin-induced dermal blood flow model, erenumab had a significant biological effect up to 8 weeks after administration of a 70-mg dose.[2] Imaging in our patient showed near occlusion of the right PCA P1 segment which subsequently resolved, suggestive of vasospasm with or without superimposed in situ thrombosis. High-resolution MR angiography during migraine attacks has demonstrated vasodilation of the intracranial arteries ipsilateral to pain, with possibly very mild vasoconstriction of some cerebral arteries occurring in response to triptan administration.[3] Shortly before her stroke, our patient used a triptan for a typical migraine. One possibility is that impairment of CGRP-mediated vasodilatory mechanisms might interact synergistically with normally mild triptan-induced vasoconstriction to produce infarction.

Whether triptans alone increase stroke risk is controversial, but both migraine and oral contraceptives are associated with increased risk.[4] Regarding the latter, our patient was using a low-dose estrogen oral contraceptive pill, which is associated with lesser risk, and had been on this for many years, whereas the risk of thromboembolic events with oral contraceptives is greatest within the first year of use.[5] Nevertheless, it is certainly possible that the association of her stroke and use of a CGRP inhibitor were coincidental, or it may be that multiple risk factors interact in an individual patient leading to stroke. Alternative stroke mechanisms, such as a partially occlusive embolism, might also explain the radiographic findings.

To date, clinical trials involving anti-CGRP drugs have not demonstrated a clear increased risk of stroke. However, these trials were limited in size and duration. Myocardial ischemia during a treadmill stress test 4 hours postsumatriptan administration and a fatal event of "atherosclerosis" were reported in the open-label extension of

the phase II trial for erenumab,[6] and a transient ischemic attack was reported in the phase II trial for eptinezumab following a supratherapeutic dose.[7]

The possibility of an association between CGRP inhibitors and stroke should be considered by physicians treating migraine. Migraine is not a life-threatening disease and stroke in a young, otherwise healthy patient can be a devastating outcome. It has been recommended that a known history of cardio- or cerebrovascular disease is a contraindication to prescribing CGRP inhibitors.[8] While this is sensible, until more extensive data becomes available, we suggest CGRP inhibitors be used with caution even in migraine patients without known vascular disease.

Conflict of Interest Statement

Stephen Aradi has no conflict; Eric Kaiser has received royalties from patents with Alder Biopharmaceuticals related to the use of anti-CGRP antibodies and antibody fragments to prevent or inhibit photophobia in migraine; Brett Cucchiara has no conflict.

References

1. Kaiser EA, Russo AF. CGRP and migraine: could PACAP play a role too? Neuropeptides 2013;47:451-461.
2. Vu T, Ma P, Chen JS, et al. Pharmacokinetic-pharmacodynamic relationship of erenumab (AMG 334) and capsaicin-induced dermal blood flow in healthy and migraine subjects. Pharm Res 2017;34:1784-1795.
3. Amin FM, Asghar MS, Hougaard A, et al. Magnetic resonance angiography of intracranial and extracranial arteries in patients with spontaneous migraine without aura: a cross-sectional study. Lancet Neurol 2013;12:454-461.
4. Roberto G, Raschi E, Piccinni C, et al. Adverse cardiovascular events associated with triptans and ergotamines for treatment of migraine: systematic review of observational studies. Cephalalgia 2015;35:118-131.
5. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, et al. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009;339:b2921.
6. Ashina M, Dodick D, Goadsby PJ, et al. Erenumab (AMG 334) in episodic migraine: Interim analysis of an ongoing open-label study. Neurology 2017;89:1237-1243.
7. Dodick DW, Goadsby PJ, Silberstein SD, et al. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol 2014;13:1100-1107.
8. Loder EW, Burch RC. Who should try new antibody treatments for migraine? JAMA Neurol 2018;75:1039-1040.