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The potential danger of blocking CGRP for treating migraine in CADASIL patients

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Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small vessel disease characterised by recurrent ischemic stroke, cognitive decline progressing to dementia, psychiatric disturbances and apathy. More than half of mutation carriers suffer from migraine, most often migraine with aura. Recently, a CADASIL patient was treated with a monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) receptor. Monoclonal antibodies targeting the CGRP system have been demonstrated to be safe, well tolerated, and effective in reducing migraine attacks. There is, however, abundant evidence that CGRP is important in maintaining cardiovascular homeostasis under (patho)physiological conditions. CGRP may act as a vasodilatory safeguard during cerebral and cardiac ischemia and blockage of the system could, therefore, potentially worsen ischemic events. Therefore, we caution against treating patients with small vessel diseases, such as the monogenic disorder CADASIL, with these drugs until relevant safety data and long term follow up results are available. Alternative preventive migraine treatments in CADASIL may be acetazolamide, sodium valproate, lamotrigine, topiramate, verapamil, or flunarizine.

Keywords

CADASIL, migraine, CGRP, stroke, patient safety

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Until recently, migraine management remained relatively unsatisfactory and without mechanistic rationale. Compounds have been developed to either inactivate the calcitonin gene-related peptide (CGRP) molecule by binding to it or its receptor, to prevent migraine from developing. These monoclonal antibodies against CGRP or its receptor are safe, well tolerated, and effective in reducing migraine attacks and headache days.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small vessel disease. CADASIL is characterised by mid-adult onset of recurrent ischemic stroke, cognitive decline progressing to dementia, psychiatric disturbances and apathy, with diffuse white matter lesions and subcortical infarcts on neuroimaging. More than half of mutation carriers suffer from migraine, most often migraine with aura (1). Migraine is the inaugural manifestation in 40% of patients. Atypical aura symptoms occur in two thirds of mutation carriers who experience migraine (1).

Recently, a middle-aged CADASIL patient was treated with CGRP-receptor monoclonal antibody erenumab for chronic migraine (2). This patient suffered from frequent migraine attacks with atypical auras consisting of visual and confusional symptomatology. The authors reported a favourable response and suggested that this may be a safe treatment for CADASIL patients.

CGRP and its receptor are abundantly present in the vasculature and maintain cardiovascular

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homeostasis under (patho)physiological conditions. CGRP may act as a vasodilatory safeguard during cerebral and cardiac ischemia and blockage of the system might, therefore, potentially worsen ischemic events. Although CGRP monoclonal antibodies seem safe, three deaths were reported in clinical migraine trials (3). During treatment with fremanezumab, two patients died (suicide and chronic obstructive pulmonary disease) (3). One patient treated with erenumab died due to an 'arteriosclerosis event' (3). Patients included in these trials were likely considered 'healthy' besides having migraine. In regular clinical practice, a 41-year old woman suffered an ischemic stroke after erenumab was started, no vascular risk factors besides combined oral contraceptive use were present (4).

For patients with increased stroke risk, including those with a monogenetic predisposition such as CADASIL, reports of ischemic events are especially troubling. It should be taken into account that CADASIL is a small vessel disease, and aberrant CGRP-mediated microvascular responses have been demonstrated in CADASIL patients (5). Blockade of the CGRP-ergic system may further increase cardiovascular risk in this patient group. Furthermore, the reported suicide is concerning as CADASIL patients are already predisposed to psychiatric illnesses. Lastly, long-term effects of CGRP blockade are still unknown.

Treatment of migraine in CADASIL is based on empirical data and personal experience. Moreover, treatment needs to take into account risk for ischemic events and psychiatric illness. From personal experience, preventive treatment focusing on (atypical) aura is most effective, including acetazolamide, sodium valproate, lamotrigine, topiramate, verapamil, or flunarizine. Depending on other headache comorbidity (migraine without aura, daily "tension-type-like" headache), candesartan or amitriptyline may be effective.

Due to the rarity of CADASIL, it is highly unlikely that enough patients can be recruited to perform clinical trials on efficacy and/or complications of CGRP-(receptor) antibodies. As an example, whether CADASIL patients should be treated with antiplatelet medication (a frequently debated subject with great relevance) still remains based on expert opinions. Nevertheless, fundamental research can provide additional information about the effect of blocking the CGRPergic system in this disorder. Recent work in healthy mice already demonstrated that blocking the CGRP system leads to worsened experimental ischemic stroke by inhibiting CGRP-mediated collateral vasodilation (6). While this may be regarded already as a warning signal that these treatments should not be prescribed to CADASIL patients, work in genetically modified CADASIL mice models will provide additional information about possible risks.

In CADASIL, ischemic events frequently occur, and their outcome could be worsened by blocking the CGRP system. Therefore, blocking CGRP may pose a risk in patients with small vessel diseases such as CADASIL and we strongly advise refraining from CGRP-blocking treatments until their long-term safety is proven.

Clinical implications

- In CADASIL, cerebral ischemic events frequently occur, and their outcome may be worsened by blocking the CGRP system.
- We strongly advise refraining from CGRP-blocking treatments in patients with small vessel diseases such as CADASIL until long-term safety is proven in case of ischemic events.
- Based on personal experience, specific preventive treatment for (a)typical migraine with aura is effective in CADASIL patients, including acetazolamide, sodium valproate, lamotrigine, topiramate, verapamil, or flunarizine.

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References

1. Guey S, Mawet J, Herve D, et al. Prevalence and characteristics of migraine in CADASIL. *Cephalalgia* 2016; 36: 1038–1047.
2. Goldstein ED, Badi MK and Meschia JF. Treating chronic migraine in CADASIL with calcitonin gene-related peptide receptor antagonism. *Neurol Clin Pract* 2019; 9: 277–278.
3. Loder EW and Robbins MS. Monoclonal antibodies for migraine prevention: Progress, but not a panacea. *JAMA* 2018; 319: 1985–1987.
4. Aradi S, Kaiser E and Cucchiara B. Ischemic stroke associated with calcitonin gene-related peptide inhibitor therapy for migraine: A case report. *J Stroke Cerebrovasc Dis* 2019; 28: e104286.
5. de Boer I, Stam AH, Buntinx L, et al. RVCL-S and CADASIL display distinct impaired vascular function. *Neurology* 2018; 91: e956–e963.
6. Mulder IA, Li M, de Vries T, et al. Anti-migraine CGRP receptor antagonists worsen cerebral ischemic outcome in mice. *Ann Neurol*. Epub ahead of print 25 June 2020. DOI: 10.1002/ana.25831.