Raynaud's phenomenon secondary to erenumab in a patient with chronic migraine

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Abstract

The case of a 45 year old female with chronic migraine undergoing treatment with erenumab 70 mg subcutaneous injection who developed Raynaud's phenomenon (RP) as a side effect with relevant clinical implications two weeks after the second dose of erenumab injection.

Introduction

Chronic migraine (CM) is a debilitating neurological disorder with a prevalence of 0.5% to 5% in the general population(1). It is associated with significant negative impact on quality of life (QOL) and mental health (2). Monoclonal antibodies targeting the CGRP pathway have been shown to be effective in episodic and chronic migraine. These molecular treatments work by binding either with the CGRP receptor or with the CGRP ligand(3). Raynaud's phenomenon (RP) is characterized by brief reduction of blood flow to the extremities due to vasoconstriction(4). The relationship of RP and migraine is previously documented. Zahavi et al. reported RP in association with migraine in 26% (29/111) of patients (4). RP secondary to administration of migraine specific therapies, such as CGRP monoclonal antibodies, has been recently reported in a few cases.

Case:

We present the case of a 45 year old right-handed lady who developed chronic daily headache (CDH) with migraine features in 2018. She had migraine headaches in her teens, often associated with her menstrual cycle. The headaches progressively increased in frequency and severity in her 30s. In January 2018, after a viral infection, she developed unremitting headache with associated migraine symptoms and chronic daily headache (CDH). The pain is usually holocranial. She also has bilateral facial pain. There is associated phonophobia, worsening with physical activity and severe fatigue. The patient denied photophobia, nausea, vomiting and cranial autonomic symptoms. Poor sleep and physical activity worsen the headaches. The clinical examination was normal, including fundoscopy. Her routine blood tests including full blood count, biochemical profile, renal, liver, thyroid function, vitamin B12 and folate were within the normal limits. MRI brain and MR venogram (MRV) of the intracranial vessels were unremarkable. The patient has a previous history of varicose vein surgery and panic attacks. Her other medication consists of duloxetine 30mg daily, paracetamol PRN and naproxen PRN.

A diagnosis of chronic daily headache (CDH) with migraine features was made in 2018, and she was started on prophylactic medication. She had failed four migraine prophylactic drugs due to side effects or lack of efficacy: propranolol (minimal benefit), amitriptyline (weight gain), topiramate (significant cognitive impairment) and

venlafaxine (worsening of headaches). Therefore, as per national and international guidelines, she was started on erenumab 70mg, monthly subcutaneous injection. The patient reported 40% improvement in headache severity and overall migraine symptoms, but with no crystal clear days.

Two weeks after the second injection of erenumab, she developed intermittent blue discoloration of both hands which worsened over a period of 7-8 months on Erenumab treatment (see Figure 1). There was no associated pain or sensory disturbance. The symptoms were worse in cold weather and improved in the summer time. Hand movements also improved the symptoms. The patient had never experienced such symptoms prior to erenumab administration. A diagnosis of RP secondary to erenumab was made. The patient initially declined discontinuation of erenumab, as she feared worsening of headaches and associated symptoms. However, she discontinued treatment after eight months due to the side effect of RP, both voluntarily and on medical advice.

Discussion:

The overall global prevalence of RP is approximately 10% in women (partly due to hormonal variations) and 4-14% in men[4]. Migraine and RP were found to co-exist in 26% (29 of 111) of migraine patients in one study [4]. Although the pathophysiology of RP is not well understood, a combination of neuronal and vascular factors (including intravascular anomalies) are known to play a role. Vasoconstriction is believed to be a major feature of RP and can be triggered by external stimuli, including cold water or weather. RP can also be triggered mainly by neural mediated changes[4].

CGRP is a ubiquitous 37 amino acid neuropeptide found in two isoforms: α- CGRP (mainly localized to the peripheral nervous system) and β- CGRP (predominantly localized to enteric nervous system). Both isoforms are efficient vasodilators [2, 3, 5]. Evidence suggests the presence of increased CGRP in sites undergoing inflammatory response[5]. Elevated CGRP levels are observed in saliva, CSF and serum during migraine attacks and reduces after these bouts subside[2]. Targeting the CGRP receptor with monoclonal antibodies is effective in the management of migraine[3, 5]. It is believed that activation of the trigeminovascular system by migraine specific triggers causes vasodilation of cranial blood vessels, thereby activating sensory nerve fibres of the trigeminal system [2, 3]. Pain is conveyed to the brainstem where several different neurotransmitters including CGRP and substance P are released, and bind to the functional receptors causing neuronal inflammation, degranulation of mast cells and leakage of blood vessels [2, 5].

Although the CGRP monoclonal antibodies, including erenumab, fremanezumab, galcanezumab, eptinezumab, were found to be safe and effective in clinical trials, more data is emerging regarding their safety profile and potential side effects in clinical practice[3]. RP is becoming a relatively rare recognized side effect of CGRP monoclonal antibodies in patients with migraine[4]. It has been recently reported in three patients (two females- 33 yrs & 45 yrs and one male- 65 yrs) undergoing CGRP monoclonal antibody treatment. Two patients were treated with monoclonal antibodies against the ligand (fremanezumab and galcanezumab) and in one case, the monoclonal antibody targeted the receptor (erenumab)[4]. There is a consensus now that the most likely mechanism by which CGRP monoclonal antibodies cause RP is primarily due to vasoconstriction, but this can only occur in conjunction with several other factors, including genetic and hormonal influences. CGRP monoclonal antibodies therefore antagonise CGRP's role as a potent vasodilator in this context [2, 3]. When administered, erenumab binds to the functional receptor, subsequently blocking its function [3, 4]. This prevents the cascade of reactions within the cell responsible for vasodilation, presumably leading to the development of RP in a small number of cases[3, 4].

In summary, we report a case of a chronic daily headache with migraine features who developed RP after receiving treatment with a CGRP receptor antagonist, further supporting the theory that RP is now a recognised rare side effect of CGRP monoclonal antibodies. This information did not emerge from clinical trials. The presence of significant or debilitating RP in a small proportion of patients with migraine who are treated with CGRP monoclonal antibodies has clinical implications, including the necessity for cessation of treatment in some patients. Furthermore, this class of drugs could exacerbate the symptoms of RP in patients with a previous history of this condition.

Clinical Implications:

Rare side effect of erenumab in treating chronic migraine

Possible side effects of MABs are to be evaluated to avoid adverse situations.

References:

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