Reduction of plasma CGRP levels in migraine patients treated with erenumab or galcanezumab

Daniel A. García-Estévez, Ana Juanatey-García, Juan Rodríguez-Garrido, Nabil Sabbagh-Casado, Gabriel Jaime-Sánchez, Laura Blanco-García

Neurology Service (D.A. García-Estévez, A. Juanatey-García, N. Sabbagh-Casado, L. Blanco-García). Clinical Analysis Service. Complejo Hospitalario Universitario. Ourense (J. Rodríguez-Garrido, G. Jaime-Sánchez). Clinical Neurosciences Research Group. Instituto de Investigaciones Sanitarias Galicia-Sur. SERGAS-UVIGO. Vigo, Spain (D.A. García-Estévez).

Correspondence: Dr. Daniel Apolinar García Estévez. Servicio de Neurología. Complexo Hospitalario-Universitario de Ourense. c/ Ramón Puga Noguerol, 52. E-32005 Ourense.

E-mail: daniel.apolinar.garcia.estevez@sergas.es

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The involvement of calcitonin gene-related peptide (CGRP) in the pathophysiology of migraine has been well established [1,2]. The appearance of monoclonal antibodies for use against CGRP in the therapeutic arsenal for migraine has been a revolution in the way in which neurologists approach the treatment of this pathology [3,4]. These monoclonal antibodies can act either by blocking the CGRP receptor (erenumab) or by binding to CGRP to reduce the amount of peptide available for binding to its receptor (galcanezumab, fremanezumab and eptinezumab). However, how CGRP plasma levels are modified by these monoclonal antibodies has only been studied to a very limited extent. A recent study determining serum CGRP levels shows a reduction in chronic migraine patients who are responders to treatment (>50% reduction in days with headache) [5], and another study with determining levels in saliva shows how depression influences CGRP levels [6]. Our research group carried out a study to ascertain the influence of treatment with erenumab or galcanezumab on CGRP plasma levels.

We studied 17 patients (two men and 15 women) with clinical criteria of high-frequency episodic migraine or chronic migraine, following the criteria set out in the third edition of the International Classification of Headache Disorders, who met the indications approved and funded by the Spanish Agency for Medicines and Healthcare Products in its therapeutic positioning report for the use of both monoclonal antibodies. Concomitant maintenance of the patient's previous preventive treatments, including botulinum toxin type A, was permitted for all patients with chronic migraine during the study period. None of the patients were diagnosed with fibromyalgia or depression. The patients were treated with erenumab or galcanezumab at the discretion of the neurologist caring for each patient, in compliance with the guidelines for routine clinical practice. A blood sample was collected inter-crisis, prior to the start of treatment and at six months of follow-up. The samples were collected in tubes with ethylenediaminetetraacetic acid, and immediately centrifuged at 3,000 rpm for 10 minutes, and then stored at −80° until subsequent determination. The CGRP plasma levels were quantified using the Abbexa -CGRP1 (CALCA) ELISA kit, with a sensitivity of 9.38 pg/mL and a range between 15.63 and 1,000 pg/mL. The test was performed on a QUANTA-Lyser 160 platform. Statistical analysis was performed with Student's *t* test for paired samples. The study was approved by our research ethics committee, and the patients gave their written informed consent to their participation in the study.

The average age of the patients at diagnosis was 47.4 ± 7.9 years old. Thirteen patients (76%) had a diagnosis of chronic migraine, and four had a diagnosis of high-frequency episodic migraine. A statistically significant reduction in CGRP levels was found six months post-treatment (21.15 ± 13.55 vs. 15.04 ± 8.05 pg/mL; $p = 0.014$). We found no significant differences in baseline and post-treatment CGRP levels between the patients treated with erenumab ($n = 9$) and with galcanezumab ($n = 8$).

CGRP has a short half-life in plasma of less than 10 minutes, which could mean that the production of this peptide remains in constant synthesis in order to sustain baseline plasma levels. CGRP has been proposed as a possible diagnostic biomarker for chronic migraine [7]. The baseline plasma CGRP levels in our study are lower than those previously reported in the scientific literature for chronic migraine, which are above 40 pg/mL [5,7]. One explanation for this finding could be the effect of concomitant treatment with botulinum toxin, as this lowers the plasma levels of the peptide [8]. Alternatively, it could be related to the molecular heterogeneity of the neuropeptides involved in migraine [9] or to the frequency of migraine attacks not related to elevated CGRP levels. The chronic migraine patients included in our study behaved as non-responders or moderate responders to botulinum toxin treatment (a reduction in the number of headache days of between 30% and 50%). This response is consistent with prior knowledge of CGRP, in that the chronic migraine patients who are most likely to behave as responders are those presenting high levels of CGRP [4,8]. As regards the effect that other neuromodulators might have on baseline CGRP levels in our patients, there is evidence to suggest that preventive treatment with topiramate and zonisamide in patients with high-frequency migraine does not modify the plasma levels of the peptide [10].

From a physiological standpoint, a hormone/peptide exerts its biological/metabolic effect by binding to a receptor, and the cascade of events that this causes at the post-receptor level represent the signals that feed back into the synthesis or inhibit production of the hormone. In the case of CGRP, stimulation of the trigeminal system leads to the antidromic release of CGRP, which acts through a G protein-coupled receptor and causes cyclic adenosine monophosphate-mediated vasodilation. A blocking of the CGRP receptor or binding to the ligand leads to a decline in the second messengers that cause that vasodilation, and consequently stimulates neuropeptide secretion [1]. At the molecular level, the action of anti-CGRP monoclonal antibodies leads to elevated plasma CGRP levels through a positive feedback effect on peptide synthesizing/secreting cells. However, the results obtained in our study and in previous studies [5,6] do not support this working hypothesis.

From a purely clinical point of view, and based on an understanding of the involvement of CGRP in the pathophysiology of migraine, it is easy to relate the clinical improvement of migraine patients to a decline in CGRP levels. Patients with high-frequency episodic migraine and those with chronic migraine who have elevated CGRP plasma levels therefore also experience a reduction in peptide levels as they become patients whose migraine is less frequent. This hypothesis is consistent with the results obtained in our study and in previous studies [5,6].

In short, our study shows a significant reduction in plasma CGRP levels in migraine patients treated with erenumab or galcanezumab.

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