



## COVID-19 pneumonia during long-term migraine prophylaxis with fremanezumab: a case report

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Dear Editor,

Migraine is a subtype of primary headache with a prevalence of 14–16% worldwide and is a leading cause of global disability under 50 years of age. Small molecule receptor antagonists (gepants), or monoclonal antibodies (mAbs) against calcitonin gene-related peptide (CGRP), have recently become available for migraine prophylaxis with proven efficacy. Although this new class of biologicals has shown a remarkable tolerability profile, their safety in the general population and under concomitant specific pathological conditions remains to be established. CGRP is highly represented in afferent nerve fibers in the lung, and seems to have a role in vasodilation of pulmonary vessels and in the attenuation of chronic hypoxia [1, 2]. On this basis, it has been hypothesized that CGRP receptor antagonism could be associated with cardiopulmonary adverse events in patients with COVID-19 [3]. Here, for the first-time, we report the outcome of a patient chronically treated (21 months) with the anti-CGRP antibody fremanezumab for migraine prophylaxis who developed mild COVID-19-related pneumonia.

A 52-year-old female nurse had personal history of ovariectomy due to endometriosis, uterine polypectomy, head trauma without loss of awareness during adolescence, and no other relevant disorders. Family history positive for migraine (*i.e.*, daughter) and no other relevant diseases.

The patient reported headache insurgence at the age of six and fulfilled the current diagnostic criteria for high frequency (8–14 attacks/ month) migraine without aura according to ICHD-3. Attacks consisted of severe, right hemicrania pulsating pain, usually accompanied by phonophobia, photophobia, and need to rest. Attacks were treated with triptans

(*i.e.*, zolmitriptan 2.5 mg) often with full pain relief. Prior preventive therapies included propranolol and amitriptyline without advantage. In 2018, she was enrolled in a clinical trial with fremanezumab. The initial randomized 3-month period was followed by a 9-month open label phase, during which she showed excellent response and no adverse events. At the end of the clinical trial, fremanezumab (225 mg monthly) treatment was maintained for migraine prophylaxis for 9 months, reporting a headache frequency of < 3 attacks *per* month and good tolerability.

In March 2020, while under fremanezumab treatment, the patient referred to the emergency room for flu symptoms. Presenting symptoms were non-productive cough, fever (> 37.5 °C), generalized weakness, and headache, followed by severe asthenia. An interstitial right pneumonia was evidenced with X-ray imaging, compatible with COVID-19. Reverse transcriptase polymerase chain reaction (RT-PCR) swab testing was positive, confirming SARS-Cov-2 infection. General and neurological examinations were normal with blood oxygen saturation  $\geq$  99%.

Complete blood workup was in range, excluding reactive C-protein (7.58 mg/dl; reference value, RV < 0.5) and white blood cell count (3700 mm<sup>3</sup>; RV 4000–11,000). Considering the overall health conditions, the absence of dyspnea and other symptoms related to pneumonia, and the emergency situation due to the epidemic outbreak, physicians proposed house quarantine. Treatment prescription was limited to 1000 mg acetaminophen on need, and periodically checking blood saturation. Fremanezumab was not discontinued. Symptoms rapidly withdrew one week after hospital admission, and two RT-PCR swabs resulted negative after one month.

Monoclonal anti-CGRP antibodies have recently been approved in the European Union for the prophylaxis of high frequency episodic and chronic migraine [4]. Their efficacy, general tolerability, and compliance associated with monthly administration, have favored their use. However, due to the ubiquitous distribution of CGRP, including

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in the pulmonary vasculature, and its protective role in systemic arterial hypertension, heart failure, pulmonary hypertension and inflammation, concerns about potential detrimental effects of long-term blockade of CGRP have been raised in COVID-19 patients with associated pulmonary and cardiovascular complications [3, 5, 6]. On the other hand, small molecule CGRP receptor antagonists have been proposed for COVID-19 treatment. A phase-II trial to test the efficacy of intranasal zavegepant, a third-generation CGRP receptor antagonist [7], in hospitalized patients with COVID-19 infection to reduce lung inflammation has been authorized by the *Food and Drug Administration* (FDA) (NCT04346615) [8]. The rationale is based on preclinical evidence that CGRP increases pro-inflammatory cytokine (*e.g.*, interleukine-6 [IL-6]) production, and T cell polarization into Th17 lymphocytes, two responses considered of relevance to COVID-19 infection [9, 10]. However, it is still unknown whether the basal or increased release of CGRP plays a role in regulating the pulmonary and cardiovascular functions in COVID-19 patients. In this regard, it is worth noting that a recent study indicates a reduced concentration of plasma CGRP in patients with COVID-19 infection [11].

Thus, the impact of drugs targeting the CGRP signaling pathway in the cardiopulmonary functions of COVID-19 patients remains controversial. No clinical studies have been reported on this topic, and only one case report has been published so far, showing no adverse events related to various treatments, including 1-year treatment with fremanezumab in a patient with suspected COVID-19 related meningoencephalitis [12]. Our report, showing that very long-term treatment (21 months) with fremanezumab 225 mg/monthly does not worsen mild pneumonia associated with SARS-Cov-2 infection in a patient who achieved a rapid and complete resolution without sequelae, appears of relevance to both CGRP and COVID-19 pathophysiology. It is also worth noting that, despite the concomitant illness, the frequency of headache attacks was unchanged. Due to the high frequency of headache in COVID-19 patients and the persistent headache symptomatology as a possible chronic sequela of the infection [13, 14], the general safety of fremanezumab in the present case could encourage the continuation of treatments with anti-CGRP molecules in these patients.

To our knowledge, this is the second case of a patient being treated with a monoclonal anti-CGRP antibody during the SARS-Cov-2 infection [12]. It is, however, the first case that reports a very long-term therapy in a patient with COVID-19-associated pneumonia. Prolonged CGRP blockade does not necessarily worsen cardiovascular/pulmonary complications COVID-19-related but the possible effect of prolonged CGRP blockade needs to be investigated. Further studies are required to assess the safety of anti-CGRP

remedies in COVID-19 patients, and their possible beneficial effects.

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## Declarations

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**Human and animal rights** This article does not contain any studies with human or animal subjects performed by the any of the authors.

**Informed consent** Informed consent was obtained from the patient to utilize her medical records for the purpose of this report. All information has been appropriately anonymized.

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