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Diaphragmatic small bowel disease in a patient with resistant migraine and medication overuse treated with galcanezumab

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ABSTRACT

Background: Monoclonal antibodies directed against Calcitonin Gene-Related Peptide (CGRP) or its receptor have greatly improved the quality of life of migraine patients. However, these treatments must be administered with caution in patients with constipation or inflammatory bowel disease, considering that non-steroidal anti-inflammatory drugs, widely used by patients with migraine to treat attacks, may have gastrointestinal side effects.

Methods: After receiving informed consent, we obtained the patient's information from her clinical documentation and archived medical records.

Results: We report the case of a patient with a clinical history of migraine with and without aura, paroxysmal hemicrania, and overuse of indomethacin, who received a diagnosis of symptomatic small bowel diaphragmatic disease under prophylactic treatment with galcanezumab. Due to the intestinal implications of CGRP, we decided to discontinue this therapy and begin OnabotulinumtoxinA treatment.

Conclusions: This case report recommends extreme caution when starting anti-CGRP mAbs treatment in patients with longstanding medication overuse with NSAIDs and abdominal symptoms.

Key words: migraine, galcanezumab, CGRP, diaphragmatic small bowel disease.

Introduction

Monoclonal antibodies directed against Calcitonin Gene Related Peptide CGRP, or its receptor (anti-CGRP/R mAbs), are markedly changing migraine treatment, as they greatly improve the quality of life of patients.[1] Several studies have now confirmed that these treatments significantly reduce headache days, pain intensity, and associated symptoms, with few side effects.[2] Among the adverse events associated with the four anti-CGRPR mAbs (erenumab, galcanezumab, fremanezumab, and eptinezumab), constipation is one of the most frequent, with different rates for different drugs.[3] Constipation results from the inhibition of the physiological function that CGRP performs in the small and large intestine, contributing to the maintenance of peristaltic motor activity, ion and water secretion, and intestinal transit.[4] Although the episodes of constipation reported in the latest published reviews are mainly mild to moderate type, anti-CGRPR mAbs should be administered with caution in patients suffering from severe constipation or associated intestinal diseases, such as inflammatory and stenotic diseases of the intestine.[5]

In addition, migraine patients often use, as acute medications, non-steroidal anti-inflammatory drugs (NSAIDs), which may have gastrointestinal side effects. In particular, the chronic use of NSAIDs seems to be related to a rather rare condition called diaphragmatic small bowel disease, which presents clinically with stenosis of the intestinal loops due to the formation of fibrous septa, predisposing the subject to intestinal obstruction.[5] We report the case of a migraine patient, overusing NSAIDs for years and more recently treated with galcanezumab, who was diagnosed with diaphragmatic small bowel disease.

Case Report

A 39-year-old woman with a history of endometriosis was diagnosed with migraine with and without aura in 2006. In the past, she used migraine prophylaxis with propranolol, amitriptyline, and topiramate, which were poorly or only partially effective in reducing migraine frequency, sometimes requiring prednisone for attack control. From 2006 to 2016, she experienced a fluctuating frequency of migraine, with periods of relative well-being alternated with an increased attack rate. Starting in 2016, she also suffered from recurrent headaches of short duration with associated autonomic symptoms, such as ptosis, ocular redness, and lacrimation, which responded well to indomethacin 50 mg. According to ICHD-3 classification, she also received a diagnosis of sporadic paroxysmal hemicrania (PH), with a period, in 2018, of higher frequency, for which a preventive therapy with indomethacin was prescribed. After 2018, this therapy was stopped, and she used indomethacin only as an acute medication to treat frequent migraine attacks. She reported long periods of overuse of indomethacin (more than 25 doses per month) as acute medication for migraine.

For the persistence of high-frequency migraine, subcutaneous monthly galcanezumab 120 mg with a starting loading dose of 240 mg was prescribed in October 2021, which provided a rapid migraine improvement. Furthermore, she presented no PH attacks during this treatment. However, 20 days after the start of galcanezumab, the patient began to complain of severe abdominal pain associated with vomiting, for which she took antispasmodics for about 20 days. She had never experienced these symptoms in the past. Blood tests showed mild hypoalbuminemia (2.32 g/dL, range 4.02-4.76), with relative increases in alpha-1, alpha-2, and beta-1 proteins and a slight decrease in gamma globulins (0.55 g/dL, range 0.8-1.35). Blood tests also showed elevated TSH (5.28 mcrUI/ml, range 0.27-4.2) and low vitamin D levels (5.4 ng/mL). A urine examination showed no significant findings. For the persistence of symptoms, the patient underwent an esophagogastroduodenoscopy (EGDS) showing cardiac incontinence and hyperemic gastropathy of the antrum related to Helicobacter pylori, for which eradication antibiotic therapy and a proton pump inhibitor were prescribed for 20 days.

However, abdominal pain with vomiting and constipation did not resolve, with progressive associated weight loss.

In December 2021, the patient underwent an abdominal CT that showed widespread distension of the intestinal loops of the small intestine, multiple air-fluid levels, and intestinal loops with signs of vascular wall congestion. The following day, the patient went to the Emergency Room with subsequent admission to the Surgery Department, where, after hydration therapy, she was discharged because of an improvement in symptoms. In January 2022, the patient underwent an entero-MRI, showing regular filling of the intestinal loops with contrast medium, marked dilatation of the ileum and colon, and concentric thickening of the ileal walls with sub-stenosis. Colonoscopy did not show macroscopic findings. However, small intestine biopsies showed signs of active inflammatory bowel disease of the ileum. Elevated values of fecal calprotectin (419.2 mg/kg) were also found. Therapy with prednisone and metronidazole was prescribed. In March 2022, the patient underwent exploratory laparoscopy with ileal resection of approximately 45 cm of intestinal loops. Pathological examination of the surgical specimen showed diaphragmatic disease of the small intestine, a morphological and clinical picture compatible with chronic overuse of NSAIDs. In June 2022, she presented herself again to the emergency room due to abdominal pain and fever of 1 week. The abdominal X-ray was normal, and the patient was discharged. She subsequently underwent an ultrasound of the intestinal loops, which showed gaseous and corpuscular distention along the entire colon in the absence of pathological thickening of the intestinal loops.

Despite the concomitant pathologies described, until October 2022, the patient did not want to interrupt the monthly administrations of galcanezumab as it had produced unprecedented and significant relief from pain and migraine days, and she completed the year of treatment. At the follow-up visit at our center in October 2022, it was decided not to renew treatment with galcanezumab. Upon discontinuation of the drug, the migraine returned to a chronic frequency, for which we prescribed treatment with onabotulinumtoxinA according to PREEMPT protocol.[6] Furthermore, we strongly advised the patient to no longer use indomethacin for the treatment of headache attacks but to prefer triptans and paracetamol. OnabotulinumtoxinA treatment provided partial benefit on migraine with an average of approximately 10 days/month of migraine. After discontinuing galcanezumab, the patient reported an occasional abdominal pain episode and was admitted to hospital several times. She eventually underwent another surgery to remove part of the small intestine.

Discussion

Anti-CGRPR mAbs are treatment for chronic and high-frequency episodic migraine with usually minor side effects.[7] Their impact on the gastrointestinal system differs according to the type of antibody; in pivotal studies, erenumab is associated with constipation (approximately 3% of patients)[8,9,10,11] compared to galcanezumab (1%),[4] and fremanezumab (<1%).[12] Published results from eptinezumab phase 3 trials do not mention constipation.[13] A retrospective study by Alex *et al.* published in 2020 on 90 patients treated with erenumab, galcanezumab or fremanazumab showed that constipation is the most frequent side effect (26.7% of the study population), but that only 4 patients (4.4%) interrupted the therapeutic cycle due to this side effect.[14] On the other hand, Robblee *et al.*, in a retrospective observational study, reported a worsening of constipation in 22.2% of inflammatory bowel disease (IBD) patients treated with erenumab.[15] An Italian multicenter real-life study on galcanezumab demonstrated that constipation and skin reactions at the injection site are the most frequent side effects of this antibody (about 2% of cases), which occur mainly in the first month of therapy and tend to resolve spontaneously.[16]

Non-steroidal anti-inflammatory drugs are widely used in the treatment of migraine attacks, and their easy commercial availability, speed of action, and effectiveness very often lead patients, especially those suffering from chronic forms of migraine, to use them in large quantities, up to the point of overuse. The use of NSAIDs may be associated with gastrointestinal toxicity, affecting both upper gastrointestinal tract (peptic ulcer disease) and lower gastrointestinal tract (NSAID-induced enteropathy). NSAIDs use has been associated with an increased risk of clinical relapse in IBD patients.[17] In a study analyzing 820 patients who have undergone upper gastrointestinal (GI) endoscopy, it was found that 14.7% of the patients resulted in having NSAIDs-related peptic ulcer.[18] In addition to upper gut complications, detrimental impact of NSAIDs on the lower gastrointestinal tract is equally crucial to the risk evaluation of these drugs. In fact, over the past decade, hospitalizations due to NSAID-associated lower gut complications have increased compared to upper gut pathologies.[19] Severe complications include luminal perforation, occult bleeding, intestinal stricture, obstructions, and ulcers.[20] Incidentally, enteric injuries are evident in approximately 71% of chronic NSAID users,[21] while a prevalence rate of direct mucosal breach has been found in around 50% of chronic NSAID users.[22] The patient illustrated in this case report has a history of chronic migraine with and without aura with periods of overuse of NSAIDs, especially indomethacin. In addition, gastrointestinal symptoms appeared only 20 days after the start of monoclonal antibody therapy, whereas the patient had been using indomethacin as a painkiller for several years. In the literature, there are no described cases of diaphragmatic small bowel disease associated with monoclonal antibodies, while this pathology is most often described in relation to the chronic use of NSAIDs.[23] However, it cannot be excluded that blockade CGRP, even if as early as 20 days from the start of treatment, somehow contributed to trigger this clinical picture, established over the years due to indomethacin overuse.

Conclusions

In conclusion, even if a correlation between galcanezumab and diaphragmatic small bowel disease is not definitively proved, this case report recommends extreme caution when starting anti-CGRP mAbs treatment in patients with longstanding medication overuse with NSAIDs and abdominal symptoms, given that blocking the CGRP pathway could facilitate an underlying intestinal dysfunction. In light of this, particular attention to the medical and pharmacological histories and close follow-up of these patients are necessary.

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