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1 **Myocardial infarction associated with erenumab: a case report**

2 Myocardial infarction associated with erenumab

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23

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25 Virginie Corand has declared conflict of interest with Lilly, Teva and Novartis. The other

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27 publication of this article.

28 **Abstract**

29 **Background:** Monoclonal antibodies acting on the calcitonin gene related peptide or its
30 receptor (CGRP-mabs) are novel drugs for resistant migraine prophylaxis. As CGRP-mabs
31 cause inhibition of vasodilatation, their use is reserved to patients with no recent history of
32 cardiovascular diseases. We report a case of myocardial infarction associated with erenumab.

33 **Case:** A 57-year-old woman with a familial history of coronaropathy, was firstly treated with
34 erenumab 70 mg for 6 months, then increased to 140 mg. Almost five months after, the patient
35 presented chest pain, increased troponin and abnormal electrocardiogram. A myocardial
36 infarction without coronarography abnormality was diagnosed through MRI.

37 **Conclusion:** Further evidences are needed to assess the risk of myocardial infarction in patients
38 treated with a CGRP-mab. In patients over 40 years, the risk of coronary or cardiovascular
39 events should be assessed using risk tables or algorithms to take into account cardiovascular
40 risk factors. This may be complemented by appropriate exams to measure the burden of
41 coronary atherosclerosis, if necessary.

42 **Keywords:** Case report, Calcitonin gene-related peptide, migraine disorder, Adverse event,
43 Pharmacovigilance, drug safety

44 ***Introduction***

45 Monoclonal antibodies acting on the calcitonin gene-related peptide or its receptor (CGRP-
46 mabs) are novel drugs indicated for the prophylaxis of migraine. They can be used in adults
47 reporting at least 4 migraine days per month and with previous failure of at least two preventive
48 drugs for migraine. To date, four CGRP-mabs are available: one targeting the CGRP receptor
49 (erenumab) and three targeting the CGRP peptide (galcanezumab, fremanezumab,
50 eptinezumab). Thanks to their prolonged inhibition of the CGRP effect, they prevent the
51 occurrence of migraine attacks (1). Their half-life is about 28 days, allowing one subcutaneous
52 injection per month.

53 CGRP receptors are expressed in the trigeminal ganglion neurons, which play a key role in
54 migraine pathophysiology by modulating the nociceptive signal (2), although CGRP receptors
55 are also ubiquitous. CGRP is the most potent vasodilator peptide known and its inhibition has
56 been theoretically considered dangerous in patients with vascular diseases. It acts via
57 perivascular innervation from the adventitia to medial layers of blood vessels, in particular at
58 arterial level (3). Its inhibition could thus reduce the vasodilatation reflex in the context of organ
59 ischemia, and potentially increase the cardiovascular risk (4-6). Pivotal clinical trials excluded
60 patients with cardiovascular and cerebrovascular morbidities, such as previous myocardial
61 infarction or unstable angina (7,8).

62 Erenumab is the first CGRP-mab marketed worldwide. In France, compassionate use of
63 erenumab is authorized only to patients free of myocardial infarction, stroke, coronary bypass,

64 angina and any revascularization procedure during the past twelve months. We report a case of
65 myocardial infarction in a 57-year-old woman four months after an erenumab dose increase.

66

67 *Clinical Case*

68 *Patient information*

69 A 57-year-old woman with a history of eardrum grafting had been a migraineur since the
70 teenage years. Here migraine attacks were initially spaced out, but had worsened in severity
71 and frequency in the last ten years in a context of increasing professional responsibilities. She
72 reported permanent pain with more than ten attacks per month on average, sometimes requiring
73 time off work. She had received numerous acute pharmacological treatments such as triptans,
74 NSAIDs, nefopam, as well as preventive medications such as betablockers, amitriptyline, and
75 oxetorone. She had also received non-pharmacological treatments like transcutaneous electrical
76 neurostimulation and acupuncture, none of which had proved efficient. Before initiation of
77 erenumab, she reported on average ten episodes of triptan use per month.

78 She had smoked for 7 years but had stopped 35 years before. She did not report any history of
79 psychoactive substance use. Her personal history was negative for cardiovascular diseases,
80 while her brother had died of coronaropathy at the age at 48 with a medical history of heavy
81 smoking, dyslipidemia, and diabetes. Her father had died of Lewy dementia, and her mother
82 had a left carotid endarterectomy in the context of dyslipidemia and diabetes and had died at
83 age 75.

84 She was enrolled in the French compassionate use program and started erenumab at 70 mg per
85 month. One month after initiation, she reported good efficacy with 23 days without migraine
86 *versus* 8 days before erenumab. She reported 4 attacks of low to moderate intensity, which
87 necessitated two doses of NSAIDs but no triptans. No strong migraine attack was reported.
88 Since promotion in her work was imminent and because the migraine attacks re-occurred, the
89 erenumab dose was increased to 140 mg per month. The patient then reported 21 days without
90 any migraine attack and a significant decrease in the use of analgesics and triptans, without any
91 recourse to triptans or NSAIDs for four months.

92

93 *Clinical findings*

94 Twenty-two days after the fourth injection of erenumab 140 mg, the patient felt a very strong
95 left supramammary laterothoracic pain without radiation during the night which was evaluated
96 at 8-9 out of 10 on a visual analog scale. The pain persisted for 6 hours and abated gradually
97 but with atypical residual pain. These symptoms were associated with sweating and diarrhea.
98 At the time of the event, LDL cholesterol was 1.91 g/L, glycemia 1.04 g/L, and blood arterial
99 pressure 100/60 mmHg. A first ECG showed a sinus rhythm with an ST elevation in the
100 inferolateral zone without a mirror pattern or an inferolateral Q-wave. The discrete ST segment
101 elevation in leads DII DIII and VF, and even in leads V5 and V6 were found only on the first
102 ECG (Figure 1). Subsequent ECGs did not evidence a Q wave but just discrete Q waves in leads
103 DII DIII and VF, which could hardly be considered as waves of necrosis. Troponin I rate on
104 day 1 was 10 000 ng/L (normal values <15.6 ng/L), 4107ng/L on day 2 and 3010ng/L on day

105 3. Myocarditis was initially suspected, but due to persistent chest pain, hospitalization was
106 decided to explore her cardiac function. At admission 48 hours after the first clinical symptoms,
107 the patient reported a persistent thoracic pain, while hemodynamic, hepatic and renal functions
108 were normal. Clinical examination was also normal, as well as brain natriuretic peptide and C-
109 reactive protein.

110 A transthoracic echocardiogram showed a normal cardiac function with no left ventricular
111 dilatation or hypertrophy, and a preserved left ventricular ejection fraction with no segmental
112 left ventricular hypokinesis, even though troponins were elevated. Coronary angiography with
113 ventriculography and aortography analyzed by three experienced cardiologists was considered
114 as normal. Cardiac magnetic resonance imaging (MRI) was then prescribed.

115 Four days later, erenumab 140 mg was injected as usual. The day after, the patient was admitted
116 to the emergency department for arm pain. Arterial doppler revealed radial thrombosis,
117 probably as a complication of the coronarography performed a few days before.

118 A few days later, cardiac MRI showed segmental hypokinesis and subendocardial perfusion
119 defects of the inferomedial segment without an intraventricular thrombus. The diagnosis was a
120 rudimentary infero-lateral myocardial infarction. As a precautionary measure, erenumab
121 treatment was contraindicated, and a second MRI was then prescribed to confirm the diagnosis
122 of myocardial infarction. Five months after the clinical event, MRI confirmed the non-
123 transmural subendocardial perfusion defect in the medial inferior territory compatible with the
124 scar of a myocardial infarction (Figure 2). The patient was thus considered as no longer eligible
125 for the erenumab compassionate use program.

126

127 ***Discussion***

128 This is the first case report of myocardial infarction in a patient with healthy coronary arteries
129 possibly related to a CGRP-mab. We applied the Naranjo scale to identify the cause of this
130 event, which was considered as probable erenumab-induced myocardial infarction (9). The
131 event occurred after an erenumab dose increase, and the confirmed diagnosis of myocardial
132 infarction with no other cardiac etiology after full exploration and previous conclusive reports
133 about the cardiovascular safety of erenumab support its role in the occurrence of this case of
134 myocardial infarction.

135 This case has some limitations: first, although the delay after infusion seemed long, it may be
136 compatible if the 28-day half-life of erenumab is taken into account. Furthermore, given that
137 she is menopausal, her increased risk of cardiovascular events in relation to her migraine disease
138 and high LDL cholesterol could be considered as confounding factors in the occurrence of this
139 myocardial infarction. Despite these limitations, the temporal relationship with the erenumab
140 injections without any triptan or NSAIDs intake reported by the patient from several months is
141 in favor of a correlation between erenumab and myocardial infarction. Moreover, although
142 radial thrombosis is a well-known complication of coronary angiography, the contributory role
143 of erenumab in its occurrence cannot be excluded.

144 This hypothesis is directly linked to the pharmacological properties of CGRP-mab, as the long-
145 term inhibition of the CGRP system may reduce the induced physiological vasodilation that
146 protects organs from ischemia, e.g. to counterbalance stress or physical effort. Since 2000s, the

147 role of CGRP in the preventing vasospasm has been demonstrated in animal models. Locatelli
148 et al. demonstrated marked vasospasm in a group of rabbits treated with anti-CGRP serum
149 versus a control group without vasospasm (10). Moreover, in their review, Marquez-Rodas et
150 al. concluded that the use of CGRP by gene therapy is promising for the prevention of
151 vasospasm following subarachnoid hemorrhage (11). In line with this, Aradi et al. described an
152 ischemic stroke in a 41-year-old woman 34 days after the first administration of 70 mg
153 erenumab. Patient imaging suggested a vasospasm mechanism and erenumab was suspected in
154 the absence of any other evident etiologies (12). Recent study-based pharmacovigilance data
155 from the World Health Organization (VigiBase®) warned about vascular safety owing to a
156 significant disproportionality signal of Raynaud's phenomenon with CGRP-targeting drugs,
157 especially erenumab (13). However, the safety profile of CGRP-mabs could be different for
158 molecules that target the CGRP receptor or ligand. Such is the case for the risk of hypertension,
159 which has been related only with erenumab (14). Further data are thus needed in order to
160 confirm the risk of myocardial infarction and if it is a class effect or specific to CGRP receptor
161 inhibitors.

162 While the theoretical cardiovascular risk of CGRP-mab has been the subject of early warnings
163 in the literature, the European Medicine Agency assessment report of erenumab included “non-
164 cardiac chest pain” as one of the most frequent serious adverse events in the treatment group.
165 A striking point is the lack of information about care, which could lead to delayed patient
166 diagnosis and care as well as an inappropriate treatment. In the event of major myocardial
167 infarction, for example, late management may mean that chances are lost for the patient.

168 Recently, a study assessing the long-term safety of erenumab *versus* placebo in 609 patients did
169 not evidence any cardiovascular risk, with adverse event rates comparable to placebo (7). Two
170 other studies based on clinical trial data concluded that erenumab did not increase the
171 cardiovascular risk compared to placebo, but both underlined the need for a longer-term follow-
172 up (15,16).

173 Even if clinical trials concerning the cardiovascular safety of CGRP-mabs are reassuring, the
174 data cannot be entirely extrapolated to the general population suffering from migraine. First,
175 the small number of patients included reduces the probability of these studies detecting
176 uncommon events. Moreover, most clinical trials excluded patients with cardiovascular
177 comorbidity such as previous myocardial infarction, unstable angina, or presence of coronary
178 artery bypass surgery. In addition, patients treated chronically with ergotamine derivatives,
179 steroids, or triptans, which can also increase the risk of cardiovascular adverse events, were
180 also excluded (7,8). To date, the only study performed on patients with established risk factors
181 (stable angina) suggested that a single infusion of erenumab 140 mg versus placebo was well
182 tolerated. Nevertheless, it was not informative concerning chronic use and was insufficiently
183 powered to detect any case of myocardial infarction (88 patients overall) (15).

184 To date, the literature concerning the cardiovascular risk related to CGRP-mabs is scarce, as
185 they are recent drugs especially used in real-life conditions. However, a recent study performed
186 on spontaneous reports of suspected adverse drug reactions collected by the USA Food and
187 Drug Administration adverse event reporting System highlighted a potential safety signal
188 concerning high blood pressure and, to a lesser extent, acute myocardial infarction (17).

189 ***Conclusion***

190 Faced with a growing request for CGRP-mabs to treat patients with resistant migraine, it seems
191 crucial to warn physicians about their potential role in the occurrence of serious cardiovascular
192 adverse events, even if there is an underlying cardiovascular risk factor. This information
193 should be delivered to all caregivers in order to provide patients with the best care after ischemic
194 disorders and avoid further exposures to the drug. Moreover, there is an urgent need to assess
195 the cardiovascular safety of CGRP-mabs in real-life conditions. In patients over 40 years, the
196 risk of coronary or cardiovascular events should be assessed using risk tables or algorithms to
197 take into account cardiovascular risk factors. This may be complemented by appropriate exams
198 to measure the burden of coronary atherosclerosis, if necessary.

199

200

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202

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