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Letter to the Editor

Is CGRP Receptor Blockade Cardiovascularly Safe? Appropriate Studies are Needed

With great interest, we read the publication by Depre and colleagues[1] describing that inhibition of the canonical CGRP receptor does not seem to worsen myocardial ischemia contrary to theoretical concerns.[2] In a randomized, double-blind, placebo-controlled study the authors did not find evidence for an adverse effect of the CGRP receptor antibody erenumab on exercise time during a treadmill test in patients with stable angina. Although we certainly appreciate the endeavor to address this important issue, we are concerned that the study population, the study design, and the interpretation of the results do not allow for such a reassuring conclusion.

While the authors rightly indicate that it is currently not clear to which extent CGRP is relevant in maintaining blood flow in case of myocardial and cerebral ischemia, we do not agree with their argument stating that "the concentrations of exogenous CGRP required to increase total exercise time or protect against myocardial ischemia far exceed the endogenous physiological levels of CGRP that are released during a response to ischemia." This is because it is not the *systemic plasma* concentration that is relevant in this perspective, but the actual concentration of CGRP *at the neuro-vascular junction*, where CGRP is released. Obviously, the plasma concentration is likely to be several log units lower than the junctional concentration due to dilution and hydrolysis. Further, we feel that the argument that erenumab does not contract the human isolated coronary artery per se[3] does not add to the introduction, since the question that should be answered here is whether inhibition of the actions of CGRP is potentially harmful in myocardial ischemia.

More importantly, the patients included in this study suffered from stable angina pectoris, which often is caused by a stenosis of the epicardial conducting portions of the coronary artery. As we pointed out earlier,[2] the importance of CGRP in the proximal, epicardial portions of the coronary artery bed seems limited, while CGRP is a highly effective vasodilator in the intramyocardial, smaller (distal) sections of the coronary artery bed. Thus, it is unfortunate that a patient population with, most likely, mainly diseased proximal coronary arteries, was chosen for this study, despite the advantage of a clear-cut definition of these patients. Although stable angina pectoris due to epicardial stenosis may occur in both men and women, this is typically considered a "male" form of cardiac pathology,[4] as illustrated by the fact that 78% of patients included in the current study were male. In contrast, in females, who are the majority of migraine sufferers and thus also the majority of the population likely to use erenumab or related drugs in future, coronary artery disease often presents as diffuse atherosclerosis, without an angiographically detectable stenosis.[4–6] These observations indicate that coronary microvascular dysfunction plays a more important role in angina pectoris in female patients and that blocking the effects of CGRP in female patients may have different effects than in male patients.

An essential concern of this study is based on pharmacokinetic and pharmacodynamic considerations. The authors rightly indicate that plasma concentrations obtained 30 min after intravenous infusion of 140 mg erenumab (the time interval until the start of the

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treadmill test) will provide "a substantial margin over concentrations achieved by subcutaneous administration of 140 mg." In contrast, their claim that "the use of 140 mg intravenous dose of erenumab ensured rapid and robust blockade of the CGRP receptor" is not substantiated by any evidence. It should be taken into account that, before a receptor blocking antibody can effectively occupy the receptor where it is binding to, the antibody should first have access to the receptor biophase. In this case, erenumab was infused intravenously and thus reached the blood vessel wall from the luminal side. The CGRP receptor is located in the smooth muscle wall,[5] thus it may take several hours before the receptor was reached by erenumab at sufficiently high concentrations to induce an effective blockade of the CGRP receptor, especially given the large molecular size (150 kDa) of erenumab. This is well beyond the time the treadmill test had finished. A way to verify whether blockade has been achieved (at least in skin blood vessels) is by assessing blockade of capsaicin-induced increases in dermal blood flow. The earliest time point for such measurements that has been published, to the best of our knowledge, for erenumab is 2 days after intravenous administration,[6] which is about 100-fold longer than the period applied in the current study. Thus, we feel that evidence for significant blockade of the canonical CGRP receptor should have been provided to substantiate the statement that CGRP receptor blockade was reached *during* the treadmill study, since otherwise the interpretation of the current study is questionable.

Taken together, we would politely urge the authors to provide evidence for the fact that vascular CGRP receptor blockade has been achieved 30 min after intravenous infusion of erenumab, since this is a crucial part of the study. Further, we plead for cardiovascular safety studies on patients and/or experimental animals with microvascular disease, as such a group may better represent the patients at cardiovascular risk after the use of erenumab. Even if the antibodies against CGRP or its receptor would not increase the risk for cardiovascular ischemia, there will be cases of patients with ischemic complaints, even without a causal relationship. Appropriate studies in relevant subjects may avoid sudden distress, such as happened with the triptans in the past.

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