CGRP ANTIBODIES WILL BECOME THE TREATMENT OF CHOICE FOR CHRONIC MIGRAINE: NO

Dimos D. Mitsikostas
Athens Naval Hospital, Athens, Greece

Calcitonin gene-related peptide (CGRP) is a potent vasoactive neuropeptide that has long being implicated in migraine pathophysiology, since early 80s. Jugular levels of CGRP are increased during migraine attacks, and intravenous CGRP administration induces migraine-like headache in migraineurs. After decoding the CGRP receptor, several CGRP receptor antagonists have been developed and all were shown to be effective for the acute treatment of migraine in a variety of large scale randomized controlled trials. Because of a number of reasons, including safety issues related to liver toxicity with chronic use, the development of CGRP receptor antagonists has shut down in most cases however, but replaced by the development of monoclonal antibodies (mAbs) targeting the CGRP pathway. These mAbs are potential future preventive anti-migraine drugs with likely improved tolerance, but questionable efficacy and safety [1,2]. Among all CGRP mAbs two are currently at phase III stage for the prevention of migraine after publication of phase II trials [3,4]. Meanwhile, novel oral anti-CGRP molecules are under investigation for the symptomatic treatment of migraine [5]. In a phase 2 trial for migraine prevention, ALD403, a novel genetically engineered humanized anti-CGRP mAb, was generally well tolerated [3]. There were no treatment-related serious adverse events and no differences in vital signs or laboratory safety data between the two treatment groups. Treatment with ALD403 resulted in a significant decrease in monthly migraine days at the primary endpoint time (weeks 5–8). In another trial, LY2951742, a fully humanized mAb to CGRP, decreased migraine headache days by 4.2 in week 12 (vs. 1.2 in the placebo group, p=0.003) [4]. No severe adverse events were observed in both trials. Placebo effect (responders rate) was similar to previous preventive trials in ALD403 (33%), but large enough in LY2951742 (45%). Nocebo effect (any adverse event in placebo treated group) was high in both trials (52-67%), higher than in oral treatments. Although these data are preliminary, the use of mAbs targeting the CGRP ligand might represent a new approach to disease-specific and mechanism-based migraine prevention. Yet safety issues remain to be answered in large-scale phase 3 and 4 trials with prolonged follow-up beyond any conclusion. Experience from mAbs in other medical conditions like multiple sclerosis is rigorous, but adverse events are theoretically acceptable in this case due to the poor prognosis of the condition. Eventually, migraine does not fit into this category. In addition, CGRP is not the single molecule involved in migraine pathogenesis. There is strong evidence that other peptides are also released during migraine and just antagonizing CGRP may be not enough to achieve an optimal efficacy for the abortive and preventive treatment of migraine [6]. In conclusion and for the moment being, available data are far away from using CGRP mAbs as first line preventive treatments in migraine, although the idea remains so attractive indeed.

References

1. *Bigal ME, Walter S. Monoclonal antibodies for migraine: preventing calcitonin gene-related peptide activity. CNS Drugs. 2014 May;28(5):389-99.*
2. *Reuter U. Anti-CGRP antibodies: a new approach to migraine prevention. Lancet Neurol. 2014 Sep;13(9):857-9.*
3. *Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, Wilks K, Kudrow D, Kroll R, Kohrman B, Bargar R, Hirman J, Smith J; ALD403 study investigators. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol. 2014 Nov;13(11):1100-7.*
4. *Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol. 2014 Sep;13(9):885-92.*
5. *Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia. 2014 Feb;34(2):114-25.*
6. *Pascual J. Efficacy of BMS-927711 and other gepants vs triptans: there seem to be other players besides CGRP. Cephalalgia. 2014 Oct;34(12):1028-9.*