MONOCLONAL ANTIBODIES ANTI-CGRP FOR THE TREATMENT OF MIGRAINE HEADACHES

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Calcitonin gene-related peptide (CGRP) is a well-studied neuropeptide of relevance for migraine pathophysiology. Jugular levels of CGRP are increased during migraine attacks and intravenous CGRP administration induces migraine-like headache in most individuals with migraine. Several CGRP receptor antagonists (CGRP-RAs) were shown to be effective for the acute treatment of migraine, validating the target for the treatment of migraine. However, for a number of reasons, including issues of liver toxicity with chronic use, the development of CGRP-RAs has yet to produce a viable clinical therapeutic.

Development of monoclonal antibodies (mAbs) targeting the CGRP pathway is an alternative approach that should avoid many of the issues seen with CGRP-RAs. mAbs are biologics, or therapeutic proteins. They are generally not subject to hepatic processing to potentially toxic metabolites. Instead, they are catabolized by normal processes to endogenous amino acids which are excreted through the kidneys or live. Overall mAbs may offer benefit over small molecules, whose metabolic profile in humans is often not fully understood until clinical testing is underway. In many cases, any toxicological issues with mAbs are due to diminished pharmacology, not to off-target effects as often seen with small molecules. What this means is that a potential mAb toxicity can be often predicted and managed, depending upon the effect of prolonged target inhibition. Accordingly, safety concerns of mAbs anti CGRP would be derived from CGRP inhibition (and therefore be non-specific to antibodies), as well as of antibody administration.

The exquisite target-specificity, prolonged half-lives, and reduced potential for hepatotoxicity and drug-drug interactions, make mAbs suitable for the preventive treatment of migraine headaches. At the time of this writing, there are three mAbs directed against CGRP in various stages of clinical development: LY2951742, developed by Arteaus Therapeutics; ALD403, developed by Alder Biopharmaceuticals; and TEV-48125 (formerly known as LBR-101), developed by Teva. In addition, there is one mAb directed against the CGRP receptor in development by Amgen (AMG 334). Two of these antibodies reported positive topline results from a Phase 2A study. No reports of liver toxicity have been disclosed. Tolerability seems to be excellent. Cardiovascular effects have not been reported.

Based upon the emerging data, mAbs targeting the CGRP pathway are a promising new drug class that may provide a valuable new option for clinicians aiming to relieve the burden of individuals with episodic or chronic migraine.