Monoclonal Antibodies Targeting CGRP

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Now more than ever is the time of monoclonal antibody use in neurology. In headaches, disease-specific and mechanism-based treatments existed only for symptomatic management of migraines (i.e., triptans), while the standard prophylactic anti-migraine treatments consist of non-specific and repurposed drugs that share limited safety profiles and high risk for interactions with other medications, resulting in rundown adherence rates. Recent advances in headache science have increased our understanding of the role of calcitonin gene relate peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP) pathways in cephalic pain neurotransmission and peripheral or central sensitization, leading to the development of monoclonal antibodies (mAbs) or small molecules targeting these neuropeptides or their receptors. Large scale randomized clinical trials confirmed that inhibition of the CGRP system attenuates migraine, while the PACAP mediated nociception is still under scientific and clinical investigation.

Keywords: calcitonin gene-related peptide ; CGRP ; erenumab ; fremanezumab ; galcanezumab ; eptinezumab

1. Introduction

Migraine is a common brain disease, classified as the second most debilitating condition and has the third highest prevalence of all medical conditions [1]. The last decade heralded a new era in migraine therapeutics. Recent advances in the field of migraine research have resulted in newly available treatment options. Among them are the anti-calcitonin gene-related peptide-receptor (anti-CGRP/R) monoclonal antibodies (mAbs). The four available anti-CGRP/R mAbs were the only disease-specific preventive agents that have the potential to change the migraine therapeutic background until now. Three of these macromolecules target the calcitonin gene-related peptide (CGRP) ligand (fremanezumab, galcanezumab, and eptinezumab), while a fourth (erenumab) targets the CGRP receptor [2][3][4]. The CGRP pathway plays a major not only in migraines, but in cluster headaches, post-traumatic headaches, fiblomyalgia and other pain conditions.

2. Erenumab

Erenumab or AMG 344 is the first anti-CGRP mAb which targets the CGRP receptor. The recommended dose is 70 mg or 140 mg every 4 weeks as a single autoinjection administered subcutaneously (sc). It is a fully human IgG2 monoclonal antibody and a potent, selective, and full competitive inhibitor of the CGRP receptor [5][6].

3. Galcanezumab

Galcanezumab or LY2951742 is a monoclonal antibody that targets and binds CGRP, therefore inhibiting its physiological activity. It is an IgG4, a 90% fully humanized antibody to CGRP [7][8][9].

It has linear pharmacokinetics and steady-state concentrations that are achieved by the first month, when a loading dose of 240 mg followed by a 120 mg maintenance dose is administered. It is unique among the four monoclonal anti-CGRP antibodies, since it is the only one that has proven efficacy as a preventive treatment of cluster headaches [10].

4. Fremanezumab

Fremanezumab or TEV48125 is a fully human immunoglobulin G2 (IgG2) delta a/kappa antibody (mAb) that selectively targets both isoforms, α and β, of CGRP. Preclinical studies using dose-dependent inhibition of intracellular cAMP release, induced by CGRP, showed that fremanezumab interferes with the ability of CGRP to bind and signal through its receptors [11].

5. Eptinezumab

Eptinezumab or ALD403 is a humanized anti-calcitonin gene-related peptide IgG1 monoclonal antibody that binds to calcitonin gene-related peptide (CGRP). It selectively binds α- and β-forms of human CGRP ligand to prevent activation of the CGRP receptor and blocks its binding to the receptor for the prevention of migraine [12]. Eptinezumab is delivered by intravenous (IV) administration (100 mg) every 3 months and has a plasma half-life after an intravenous infusion of 100 mg of 31 days.

6. Approvals

Erenumab was approved in the US for the preventive treatment of migraines in adults, based on positive Phase II and III results. It has also received a positive opinion in the EU for the prophylaxis of migraines in adults who have at least four migraine days/month. Erenumab was the first anti-CGRP/R mAb that was globally approved by both FDA and EMA for migraine prevention in 2018 [13]. The FDA approved galcanezumab as a once-monthly subcutaneous injection for the preventive treatment of migraines in adults in September 2018. The EMA also issued, for the prophylaxis of migraine in adults who have at least four migraine days/month, a positive opinion regarding the use of galcanezumab [14]. The agent has been tested in cluster headache prevention in two trials and it is approved for cluster headache prevention by the FDA but not by the EMA [15]. In September 2018, fremanezumab was also approved by the US FDA for the preventive treatment of migraines in adults and later on by the EMA [16]. In February 2020, eptinezumab, the first IV administered anti-CGRP/R mAb, was approved in the USA for the preventive treatment of migraine in adults and is under review by the EMA [12].

7. Guidelines for the Use of mAbs in Migraine (American Headache Society/European Headache Federation)

The American Headache Society (AHS), published, in 2018, a consensus position statement on integrating new migraine treatment into clinical practice [17]. It provides guidelines and indications for initiating treatment with anti-CGRP/R mAbs to achieve cost-effective care. Specifically, anti-CGRP/R mAbs initiation is recommended in patients with debilitating low-frequency EM, high-frequency EM or CM and intolerance or inadequate response to a 6-week trial of at least two preventive medications (e.g., topiramate, valproate, beta-blockers, tricyclic antidepressants, serotonin and noradrenaline r inhibitors (SNRIs)). Another recommendation in CM patients is inadequate response to a minimum of two quarterly injections (6 months) of onabotulinumtoxinA or inability to tolerate the treatment. AHS recommends assessment of the benefits of anti-CGRP/R mAbs after 3 months of treatment for those administered monthly and 6 months for those with quarterly administration of the treatment and the headache specialists may continue their administration only if treatment benefits are documented.

In 2019, the European Headache Federation (EHF) published guidelines on the use of monoclonal antibodies acting on the calcitonin gene-related peptide or its receptor for migraine prevention [18]. EHF found low-/high-quality evidence to recommend eptinezumab, erenumab, fremanezumab, and galcanezumab in patients with EM and medium-/high-quality evidence to recommend erenumab, fremanezumab and galcanezumab in CM patients. EHF (Expert Opinion Statement) recommends initiation of available anti-CGRP/R mAbs in patients with EM or CM who have failed at least two of the available medical treatments or who cannot use other preventive treatments due to side effects, poor compliance or comorbidities. EHF recommends a longer monitoring period than AHS and treatment discontinuation if there are not specific benefits recorded after 6–12 months. It is also stated that, in patients with CM and MOH, the use of anti-CGRP/R mAbs can be initiated before or after withdrawal of acute medications. Several national headache societies have published recommendations on the use of anti-CGRP/R mAbs for migraines [19][20][21].

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