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Editorial

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Targeting Calcitonin Gene-Related Peptide and its Receptor by Monoclonal Antibody, New Developments in the Prevention of Migraine

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Migraine is a chronic headache disorder with an unknown pathophysiology. Research in the past decade has shown that to be a brain disorder, a dismodulation of sensory processing affecting vascular tone and pain[1-3] but since the exact pathomechanism of migraine is not very well known, its treatment is also difficult. Current drugs recommended by the "European Federation of Neurological Societies (EFNS)" used in the treatment of migraine include the triptan family drugs that are serotonin (5-$HT_{1B/D}$) receptor agonists, and the Non-Steroid Anti-Inflammatory Drugs (NSAIDs).[4] Several other drugs such as anti-epileptic drugs, beta-blockers, and calcium channel blockers are also recommended in the treatment of migraine.[4]

Although glutamic acid is one of the main neurotransmitters in the sensory system, various neuropeptides have been implicated in pain but among them, Calcitonin Gene Related Peptide (CGRP) is the only one neuropeptide that was found elevated in the blood of migraine patients[5-7] and CGRP administration induces migraine-like attack in migraine patients.[8] Therefore, several studies in the last decade focused on drugs to block the CGRP receptor[9-11] or the effect of CGRP itself by antibodies against it[10-12] although, it is not clear if the site of action of these drugs is peripheral or central.[13]

Nevertheless, triptan family drugs are currently some of the best and most potent compounds in the treatment of migraine,[4,14] but not all patients respond to them and search for other drugs that lack vasoconstrictive activity has continued. The discovery of CGRP-receptor antagonist drugs,[15] the so called "gepant family drugs" such as telcegepant and olcegepant, and BI 44370 TA were the main events in migraine research in the last decade.[16-21] Unfortunately, these drugs were discontinued due to their side effects such as hepatotoxicity although they were able to treat migraine effectively. Nevertheless, some newer drugs in this category including MK-3207,[22,23] BMS-846372[24,25] and MK-1602[26] are still under investigation, see[10] for a brief review. Nevertheless, research in the treatment of migraine did not stop here and search for other drugs being able to block CGRP or its receptor continued.

CGRP receptor is a hetero-oligomeric complex that has a peculiar structure and consists of a component, called the "Calcitonin receptor-like receptor (CLR)" which is a transmembrane Gs protein-coupled receptor, and an accessory protein component known as the "Receptor Activity-Modifying Protein 1 (RAMP1)" for the transport of CLR to the plasma membrane, and another component known as "Receptor Component Protein (RCP)" that is important for signaling pathway by determining the G-protein to which the receptor should be coupled with.[10,27,28]

In recent years, monoclonal Antibodies (mAbs) against CGRP or its receptor have been developed and are the newest anti-migraine drugs in clinical trials.

Monoclonal Abs against CGRP remove the excess peripheral CGRP that is released from the perivascular nerve endings and mAb against CGRP receptor prevents the CGRP signalling cascade.[10-12,29-31] Please see[31] and corresponding references for a brief review of the structure of CGRP and its receptor and related signalling molecules.

At the moment, there are three anti-CGRP mAbs examined in clinical trials. These include the LY2951742 that has been developed by Eli Lilly and Company,[32] ALD-403 that has been developed by Alde Biopharmaceuticals[33] and TEV-48125 (LBR-101), developed by Teva Pharmaceuticals.[34] The other class of mAb is against CGRP receptor complex, the AMG 334 that has been developed by Amgen.[35]

Although these drugs are still in clinical trials, LY2951742 and ALD-403 have both shown to decrease the mean migraine days per month from baseline compared to placebo group.[36,37] The LY2951742 is a humanized mAb against CGRP with a half-life of 28 days and was given subcutaneously (150 mg once every 2 weeks for 12 weeks) to migraine patients. Migraine days decreased from 4-14 days per month. This decrease was 4.2 days in drug treated group compared to the placebo treated group who had 3.0 days decrease in headache days per month in the 3rd month;[36] that is 1.2 day difference in migraine headache although, there this decrease was evident from the first month.[36]

The ALD-403 is also a humanized mAb against CGRP with a half-life of 31 days and was given as a single i.v. dose (1000 mg per 3 month).[37] Migraine days decreased from 9-10 days of headache per month that 8-9 of them qualified as migraine days. This decrease was 5.6 days in drug treated group compared to the placebo treated group who had 4.6 days decrease in headache days per month in the 3rd month;[37] that is 1 day difference in migraine headache nevertheless, decrease in migraine days started from the first month.[37] TEV-48125 (LBR-101) is also a humanized mAb against CGRP that has a half-life of 45 days. It has been used at 0.2- 2000 mg given in a one hour i.v. infusion as a single dose once on day 1, or up to 300 mg twice on day 1 and 14. It is now in clinical trials phase 2 and has been reported to reduce the migraine days.[12,38] The phase 2b clinical trials will be based on a 1-month run-in phase which is followed by one subcutaneous injection per month for 3 months.[12]

The other drug in this category is the AMG 334, a mAb against CGRP receptor. It is under clinical investigation and analysis but reduction in migraine days per month has been reported.[39]

Please see[10-12,31] for brief review of the drugs against CGRP and its receptor and some of the biological activities of CGRP.[31]

Another interesting pathway is activation of Vanilloid receptor 1 (transient receptor potential action channel subfamily V member 1, TRPV1) and release of sensory neuropeptides such as CGRP.[40] Similarly, inflammatory conditions can activate the TRPV1 receptor resulting in CGRP release[41] therefore, blocking TRPV1 has been one of the goals of some scientists in the treatment of pain in the last couple of years.[42,43]

Inhibition of TRPV1 receptor or interfering with the CGRP effect improves health and increase longevity in mice.[44] Can mAbs against CGRP has other effects?

Nevertheless, in addition to targeting CGRP or its receptor with mAbs several other new drugs in clinical trials such as 5-HT_{1F} receptor antagonist, drugs targeting nitric oxide synthase, glutamate, or GABA-A as well as invasive and noninvasive neuromodulation are under investigation for the treatment of migraine, please see[45,46] for review.

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