NEURO

Openventio PUBLISHERS

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-117

Review

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Volume 2 : Issue 3
Article Ref. #: 1000NOJ2117

Article History
Received: September 10th, 2015
Accepted: October 6th, 2015
Published: October 7th, 2015

Citation
Samsam M. Drugs against calcitonin gene-related peptide and its receptor used in the treatment of migraine: What are the new progresses? *Neuro Open J*. 2015; 2(3): 79-91. doi: 10.17140/NOJ-2-117

Drugs Against Calcitonin Gene-Related Peptide and its Receptor Used in the Treatment of Migraine: What are the New Progresses?

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ABSTRACT

Migraine is a chronic headache disorder that its exact pathomechanism is not very well known but research in the last two decades indicates that it might be a brain disorder, a dismodulation of sensory processing of the brainstem responsible for regulation of vascular tone and the pain. Several neurotransmitters and neuromodulators including neuropeptides have been implicated in the pathomechanism of migraine, among them, Calcitonin gene-related peptide (CGRP) has been the focus of many studies in recent years. Increased CGRP level (perhaps due to release from peripheral and central sensory nerve endings) has been detected in the blood of migraine patients and many basic and clinical investigators in recent years have been trying to block the CGRP receptor by means of newly developed CGRP-receptor antagonist drugs or inhibit its activity by even newer compounds, the monoclonal Antibodies (mAbs) against CGRP or its receptor. These latter ones are still in clinical trials but have had promising results so far in alleviating the pain of migraine patients. This article will briefly review and discuss the role of CGRP and its receptor in migraine and some of the other biological activities of CGRP, the CGRP receptor antagonist drugs and the new progresses in mAbs against CGRP or its receptor.

KEYWORDS: Migraine; Calcitonin gene-related peptide.

ABBREVIATIONS: CGRP: Calcitonin gene-related peptide; mAbs: monclonal Antibodies; TG: Trigeminal Ganglion; NSAIDs: Non-steroid anti-inflammatory drugs; CLR: Calcitonin receptor-like receptor; RAMP1: Receptor activity-modifying protein 1; RCP: Receptor Component Protein; TNF: Tumor Necrosis Factor; IL-10: Interleukin-10; TLR4: Toll-like receptor 4; eNOS: endothelial Nitric Oxide Synthase; ASD: Autism Spectrum Disorders; RNA: Ribonucleic acid; BBB: Blood Brain Barrier.

INTRODUCTION

Migraine is believed to be a brain disorder, a deficiency of sensory modulation, and probably a system failure of normal sensory processing of the brainstem that regulates the vascular tone and the pain in migraine.[1,2] Although the aura phase of migraine is believed to be due to cortical spreading depression, a similar mechanism of neuronal excitation is believed to be the trigger for migraine while the headache phase of migraine seems to involve the trigeminovascular system consisting of mainly trigeminal nerve and meningeal vessels.

Observations of Dr. Goadsby and several investigators using imaging studies suggest that the trigger phase of migraine is initiated by neuronal hyperexcitability and activation of the brainstem, hypothalamus, and the brain, and that activation is often unaffected even after relief of the headache by antimigraine drugs.[3-5]

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-117

A major part of the dura mater specially the supratentorial part of dura is innervated by the trigeminal nerve, mainly the ophthalmic branch. The Trigeminal Ganglionic (TG) neurons contain several neurotransmitters and neuromodulators among them glutamic acid and various neuropeptides including the calcitonin gene-related peptide.[6,7] Several neuropeptides coexist together in TG sensory neurons and may be released at the first central trigeminal synapses in the brainstem upon stimulation,[8] but clinically, significant CGRP increase has been seen in migraine patients.[9,10] CGRP administration in human provoked a migraine-like attack in migraine patients[11] and CGRP-antagonists alleviated the headache to a comparable level to other potent anti-migraine drugs such as sumatriptan.[12] Currently, some of the first choice antimigraine drugs include the triptan family drugs that are the serotonin receptor agonists (5-$HT_{1B/D}$), and the Non-steroid anti-inflammatory drugs (NSAIDs) according to the "European Federation of Neurological Societies (EFNS)".[13] Please see[14-16] for a comprehensive review of the triptan family drugs and their receptors, and see[5,17] for a brief review of several other drugs that are being used for the treatment of migraine including their actions, effects and side effects.

However, research in the treatment of migraine is one of the active fields of the neurological research and several studies in recent years focused on new and alternative treatment strategies including antagonizing CGRP receptors and/or blocking the CGRP activity by mAbs against CGRP and/or its receptor.

Calcitonin gene-related peptide consists of 37 amino acid detected by alternative processing of Ribonucleic acid (RNA) transcripts from the calcitonin gene which result in the production of distinct messenger RNA (mRNAs) that encodes the hormone calcitonin.[18]

There are two forms of CGRP in humans: the α-CGRP and the β-CGRP that are derived from different genes that differ in 3 amino acids but show similar functions.[19] The α-CGRP is expressed in sensory neurons including the trigeminal ganglion and is the relevant one in migraine pathophysiology while the β-CGRP is expressed in the enteric nervous system and in hypophysis and its role in migraine is not known.[20-22]

There is a wide anatomical distribution of CGRP in the body including the central and peripheral nervous system and is involved in many functions including nociception, glucose uptake, and stimulation of glycolysis in the skeletal muscles.[23] CGRP is a potent vasodilator in human and rat and may mediate hyperemia in some pathological conditions.[24]

The headache phase of migraine is believed to be caused by vasodilation of cranial vessels activating the trigeminal and other sensory nerves,[25-28] although migraine has been reported without the initial dilatation of the middle cerebral artery[29] and even during cerebral hypoperfusion.[29-32]

CGRP Receptor and its Localization in the Nervous System

CGRP receptor has an unusual structure and consists of a hetero-oligomeric complex with a transmembrane Gs protein-coupled receptor, the "Calcitonin receptor-like receptor (CLR)" and an accessory protein known as the "Receptor activity-modifying protein 1 (RAMP1)" which is necessary to transport CLR to the plasma membrane. Both the CLR and RAMP1 subunits have extracellular domains that interact with one another and together form a complex for the peptide-binding site.[33-36] The extracellular domain of RAMP1 is very important for the binding of CGRP-receptor antagonist molecules to the CGRP receptors[37] and function of RAMP1 is crucial for the activity of CGRP receptor in the trigeminal ganglion.[38] Another related structure of the CGRP receptor is the Receptor Component Protein (RCP) which is crucial for signaling pathway and determines the G-protein to which the receptor should be coupled with.[29,35]

The CLR acts as a receptor for either CGRP or adrenomedullin, depending on which members of RAMPs are expressed. RAMP1 is a CGRP receptor at the cell surface and acts as a mature glycoprotein as well. RAMP2-transported receptors are adrenomedullin receptors and are core-glycosylated molecules.[33,39]

Although originally two CGRP receptors (1 and 2) were recognized[40] the nomenclature changed later and the "CGRP(1)" receptor is now known as the "CGRP" receptor.[17,41]

Various signaling molecules and second messengers are involved following the CGRP receptor activation. These include the CGRP activation of ATP-sensitive K^+ channels[42] or large-conductance Ca^{+2}-activated K^+ channels[43] with a subsequent increase of intracellular cAMP[44] leading to vasodilation and headache. Nitric oxide activation of CGRP release in trigeminal ganglion neuronal cell culture however involves extracellular calcium and T-type calcium channels.[45]

CGRP receptor (both CLR/RAMP1 components) mRNA and protein are expressed in several regions of the CNS including the spinal cord and spinal trigeminal nucleus, area postrema, pineal gland, parts of hypothalamus, periaqueductal gray matter, pontine raphe nuclei and the gracile nucleus although the RAMP1 mRNA was also detected in several regions of the brainstem and that CGRP receptor was found in areas that were not supported by BBB.[46]

CGRP receptor is also expressed in the cerebellum.[47] Localization of the CGRP receptor in the tigeminovascular system seems to be on the central trigeminal nerve endings, dural blood vessels and mast cells, and trigeminal ganglion[48,49] as well as dorsal horn secondary neurons.[50] Please see[22,46,51] for a comprehensive review of the CGRP receptor sites. CNS glial cells such as astrocytes and microglial cell[52] and Schwann cells[49] also express CGRP receptors as well.

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CGRP Receptor Antagonists in the Treatment of Migraine

One of the important properties of CGRP-antagonist drugs such as BIBN4096BS is that it prevents the CGRP-mediated vasodilation or activation of trigeminovascular afferents[53] without the vasoconstrictor activities which is an advantage in patients with coronary heart disease or in patients with second rebound attack, see[53,54] for review.

The discovery of CGRP-antagonist drugs the "gepant" family, in the last decade was a breakthrough in migraine treatment research due to their lack of vasoconstrictive activity compared to some "triptan" family drugs. One of the first drugs, the BIBN4096BS, also known as olcegepant, prevents the CGRP-mediated vasodilation or activation of trigeminovascular afferents,[12] and presumably inhibits the central CGRP receptors.

Olcegepant is a potent anti-migraine drug that has been examined on human arteries.[55-59] The BIBN4096BS was shown to block the responses evoked by stimulants such as α-CGRP and capsaicin, or transcranial electrical stimulation of perivascular trigeminal nerve[60] which reduces the increased dural blood flow without changing basal vascular parameters,[61,62] whereas sumatriptan reduced only the vasodilation induced by electrical stimulation.[17,60] One important advantage of olcegepant over the triptan family drugs is that it doesn't constrict the coronary arteries.[55,63,64]

Olcegepant has been shown to inhibit CGRP receptor in the trigeminal nucleus suggesting a similar central nervous system mechanism as well in treatment of migraine.[65] Another drug in this class, the MK-0974 (telcagepant) is another effective CGRP receptor antagonist when administered orally for the acute treatment of migraine.[66]

Both olcegepant (iv) in phase I, phase II and telcagepant (oral) in phase III have been used in migraine clinical trials.[66-69] The efficacy of the CGRP antagonists in the central modulation of pain in the hypothalamus has also been reported by Goadsby and colleagues.[5,70] A major side effect of these drugs is hepatic toxicity and elevated transaminase levels[71] although the presumably high doses of olcegepant and telcagepant alleviating the migraine symptoms are not so high after all.[72] A newer CGRP antagonist "BI44370TA" was reported to have a lower frequency of adverse effects in its phase II clinical trials.[73] It seems that the CGRP antagonists can act on CGRP receptors however it is uncertain whether they act on peripheral or central sites or both in migraine.[72]

Please see[74-77] for a comprehensive review on the CGRP and its functions, receptors, and the implication of CGRP-receptor antagonists as a novel approach in the treatment of migraine attacks. A recent report comparing the dose-response curve for the efficacy and adverse effect of several serotonin receptor ($5\text{-HT}_{1B/D}$) agonist drugs such as triptans or Lasmiditan (5-HT_{1F} antagonist) and the CGRP-receptor antagonists such as telcagepant, BI44370TA, MK-3207, and BMS-927711 indicates that the dose-response curve for efficacy of triptans is flat while their adverse effects increase by increasing the doses. While Lasmiditan and the CGRP-receptor antagonist drugs had also a flat dose-response curve, the efficacy-tolerability profile of the triptans is more favorable than others.[78]

Nevertheless, these newer drugs may have advantage in those patients that are triptan non-responders or with coronary heart disease or in patients with second rebound attack.[53,54,78] So far five different CGRP-receptor antagonist drugs with proof of efficacy have been used for the treatment of migraine but were discontinued due to hepatic toxicity and other side effects.[79-82]

Therefore, search for newer drugs against CGRP did not stop but this time, efforts were on developing antibodies against CGRP and it receptors.[83,84]

Monoclonal Antibodies against CGRP and its Receptor in the Treatment of Migraine Headaches

Antibodies against viruses have long considered as effective preventive methods in viral infections.[85,86] Antibodies against biological antigens (in this case, CGRP) can bind proteins and neutralize their effect (block the activity) whether being free in the circulation or membrane-bound and possibly intracellular proteins.

Monoclonal antibodies (mAbs) against CGRP and its receptors are newer drugs that have emerged in recent years[87] Table 1. Several investigators have been studying three mAbs for the prevention of episodic migraine and one mAb for the prevention of chronic migraine in the last couple of years.[87] The main idea was to remove the excess peripheral CGRP released from the perivascular nerve endings and for the anti-CGRP receptor antibodies to prevent the CGRP signalling cascade.[82,83]

Currently, three anti-CGRP mAbs have been developed that are in clinical trials. These include the LY2951742 (by Eli Lilly and Company), ALD-403 (by Alde Biopharmaceuticals) and TEV-48125 (LBR-101) developed by Teva Pharmaceuticals. The other class of mAb is against CGRP receptor complex, the AMG 334, developed by Amgen.

The ALD 403: Is a humanized Anti-CGRP mAb that has been used for episodic and chronic migraine, please see company's website.[88] It has completed phase 1[89-90] study and is in phase 2.[91] It has a half-life of approximately 31 days and has finalized positive proof-of-concept in phase 2a with a single i.v. dose of 1000 mg that can be repeated every 3-month.[92] The safety of the drug was assessed at 12 weeks after the infusion; the primary efficacy endpoint was observation of changes in the frequency of migraine days from the baseline to weeks 5-8 among adult patients age 18-55 years who had 9-10 days of headache per

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-117

Drug: action	Dose; Half -life	Decrease in migraine days per month from baseline compared to placebo group	Reference
The ALD 403: mAb against CGRP	1000 mg per 3 month (single i.v.dose); Half-life: 31 days	5.6 in drug treated *versus* 4.6 days in placebo group (1 day difference) in the 3rd month.	92
LY2951742: mAb against CGRP	150 mg once every 2 weeks for 12 weeks (subcutaneous dose); Half-life: 28 days	4.2 in drug treated *versus* 3.0 days in placebo group (1.2 day difference in migraine headache) in the 3rd month.	94
TEV-48125: mAb against CGRP	0.2- 2000 mg (a one hour i.v. infusion) as a single dose once (on day 1), or up to 300 mg twice (day 1& 14); Half-life: 45 days Phase 2b clinical trials will use a 1-month run-in phase followed by one subcutaneous injection per month for 3 months	Still under investigation and analysis but reduction of both headache hours and days per month was reported.	82,104,105
AMG 334: CGRP-receptor mAb	Subcutaneous injection	Still under investigation and analysis but reduction in migraine days per month in episodic migraine patients was reported.	114,115

Table 1: Monoclonal antibodies (mAbs) used in clinical trials against CGRP or its receptor in the treatment of episodic and/or chronic migraine.

month where 8-9 of them qualified for migraine days.[82,92] Patients treated with ALD403 had a mean decrease of 5.6 migraine days between baseline and weeks 5-8 compared to the placebo group who had a decrease of 4.6 migraine days in the 3rd month (1 day difference).[82,92] The difference in the first month was 5.6 *versus* 3.9 days between the ALD403 group and the placebo (1.7 days difference).[82,92] These results showed the efficacy of ALD403 and there was no safety concern with the i.v. injection of 1000 mg of this mAb against CGRP.[92] Some side effects included infections of the upper respiratory, or urinary tracts, back pain, fatigue, nausea and vomiting that were seen in 57% of the 81 patients treated with ALD403 but were also seen in 52% of the 82 individuals who received the placebo treatment.[92]

LY2951742: Is another humanized anti-CGRP mAb (Lilly's clinical development pipeline)[93] with a half-life of 28 days[94] that has completed phase 1 clinical trials for the treatment of episodic and chronic migraine[95,96] and was tested in phase 2 clinical trials.[97] This phase 2 proof-of concept included randomized, double blind, placebo controlled investigations in 35 centres in the United States.[94]

The safety of the drug was assessed at 12 weeks treatment period after subcutaneous administration of 150 mg of this mAb twice per month (once every 2 weeks) for 12 weeks.[94] The primary endpoint was observation of changes in the number of migraine headache days per 28-day period that were evaluated at 9-12 weeks (although follow up assessment continued over 24 weeks as well) among adult patients age 18-65 years having 4-14 days of migraine headache per month.[94] Patients treated with LY2951742 had a mean decrease of 4.2 (62.5% decrease) migraine headache days between baseline and week 12 compared to the placebo group who had a decrease of 3 migraine days (42.3%).[94] This study indicated that LY2951742 may be beneficial in prevention of migraine.[94]

Adverse effects such as pain and erythema or both at the injection site (20% *versus* 6% in placebo group), upper respiratory tract infections (17% *versus* 9% in placebo group) and abdominal pain (6% *versus* 3% in placebo group) were more frequent in the LY2951742 treated group than the placebo treated group.[94] Another effort was also determining the dose selection for phase 2 studies.[98] LY2951742 is currently in clinical trial phase 3 for treatment of episodic cluster headache.[99]

TEV-48125: Also known as LBR-101 (with a former identity: RN-307) is also a humanized anti-CGRP mAb for treatment of episodic and chronic migraine (Teva Pharmaceutical Industries Ltd.)[100] and has a half-life of about 45 days, the longest among the anti-CGRP mAbs.[101] Its safety profiles were demonstrated through six phase one studies.[102] Studies in monkeys established the safety and tolerability of LBR-101 and appeared to have no significant effect in cardiovascular and haemodynamic parameters.[103] Clinical studies used 0.2-2000 mg given as a single dose (a one hour i.v. infusion) once (on day 1), or up to 300 mg given twice (day 1 and day 14) to human subjects.[104] These doses were well tolerated and overt safety concerns were not noticed.[82] TEV-48125 is currently in two phase 2b clinical trials, administered as a 1-month run-in phase followed by randomization and monthly subcutaneously injections for 3 months.[82] TEVA company announced the successful completion a phase 2b clinical trial using TEV-48125, meeting the primary and secondary endpoints in both chronic and episodic migraine study after a single dose injection which was significantly higher than placebo and resulted in significant reduction of both the number of monthly cumulative headache hours, and the number of headache days of at least moderate severity relative to baseline.[105] No significant cardiovascular or liver function adverse effects were seen compared to the placebo receiving control group, please see[82,104] for details of the studies and a comprehensive review.

AMG 334: Is a CGRP-receptor mAb, indicated in Amgen media news release[106] that has completed phase 1[107-109] and is in its phase 2 clinical trials.[110-112] A few recent reports[113] and those of Amgen

released results (reported by PRNewswire) of a global phase 2 clinical trial (which was also presented in the 17th congress of the International Headache Society, Valencia, Spain) indicate that this fully human mAb, the AMG 334 seems to have significantly decreased the mean migraine days per month in episodic migraine patients.[114,115] These studies are currently ongoing but please see references[112,113] for more details of AMG 334 studies that has been released so far.

Biological Role of CGRP in Homeostasis

So far we discussed the CGRP being a neurotransmitter/neuromodulator that mediates vasodilation peripherally and acting on its receptor on central neurons but it is important to discuss some other biological roles of CGRP in the body.

In the lung and respiratory airways, in addition to CGRP expression of the sensory neurons innervating the airways, blood vessels and lymphoid tissue,[116] CGRP is also localized in specialized epithelial (neuroendocrine) cells in the lungs and is involved in regulation of vascular tone,[117] protection of the bronchial tree, the anti-inflammatory responses and tissue repair.[118] Ablation of sensory nerve fibers leads to a significant increase in inflammatory responses, and congenital CGRP-knockout mice have increased reperfusion-induced tissue inflammatory activities.[119] In the gastrointestinal (GI) tract, stimulation of sensory nerves reduces reperfusion-induced liver injury and stressed-induced gastric mucosal injury in rodents presumably by CGRP-induced increase in the expression of prostacyclin [PGI(2)] and attenuation of inflammatory responses such as tissue Tumor Necrosis Factor (TNF) increase and tissue accumulation of neutrophils.[119]

CGRP is a negative regulator of innate immune responses by inhibiting the antigen presenting cells such as macrophages and dendritic cells, blocking their capacity to produce proinflammatory cytokines.[120,121] This effect of CGRP is mediated by production of Interleukin-10 (IL-10) and IL-10 independent processes that stimulate the expression of the inducible cAMP early repressor (International Confederation of Energy Regulators (ICER)) and inhibition of NF-$_{K}$B, although in sepsis this effect of CGRP may complicate the situation.[121] A central role for intestinal dendritic cells in neuroimmune communication and similar roles for neuropeptides including CGRP in the skin, lung and GI tract has also been proposed.[122]

The Toll-like receptor 4 (TLR4), a bacterial gram negative receptor, can activate the Vanilloid receptor 1 (transient receptor potential action channel subfamily V member 1, TRPV1) and result in the release of CGRP and its anti-inflammatory effects in the intestine.[123]

CGRP expressing nerve fibers in the GI tract are involved in pain, GI motility and secretion, defense against irritants, and wound healing of ulceration, presumably acting *via* TRPV1 receptor.[124] The central action of CGRP controls the GI motor function and intestinal motility including the migrating motor complexes.[125]

CGRP and TRPV1 (and some other neuropeptides and receptors/channels) are also involved in the neural plasticity of almost all parts of GI tract including the liver and pancreas during pathological conditions.[126]

CGRP release from the mesenteric perivascular nerve fibers increases the induction of pannexin-1-formed channel opening (hemichannels) which results in reduction of pannexin-1 and endothelial Nitric Oxide Synthase (eNOS) expression, and CGRP blockade increases the eNOS expression significantly.[127] These channels are important in the regulation of blood brain barrier as well.

There are evidences that CGRP expressing fibers of trigeminal ganglion innervate the pineal gland in several mammalian species.[128] Pineal gland is known to regulate hypothalamus, the command center for the control of autonomic and endocrine activities. Although this might be involved in the autonomic responses of pain following activation of the trigeminovascular system.

There is even a role for CGRP in the neuromuscular transmission. CGRP seems to significantly stimulate the calcium (Ca^{++}) channels at the sarcoplasmic reticulum leading to Ca^{++} release into the cytosol of the skeletal muscle and also stimulate the Ca^{++} channels at the sarcolemma to a lesser extent.[129]

CGRP expression increases in injured motor neurons and is believed to activate neuroglial cells such as astrocytes and microglial cells in the CNS which is believed to be responsible for tissue remodeling and repair.[52]

DISCUSSION

Several anti-migraine drugs have been developed in the past three decades. Tremendous efforts by brave scientists, clinicians, drug companies, and patients (for clinical trials) in this field has contributed to the significant achievements so far and this effort continues until various treatment options for migraine are found.

Although CGRP has several important roles in human body, increases in its levels in the blood of migraine patients has been linked with the headache. Therefore, inhibiting its activities by means of CGRP-receptor antagonists and/or monoclonal antibodies against CGRP or its receptor has been a focus of more than a decade of research to find another alternative treatment to alleviate the pain of migraine specially on those who are non-respondent to other drugs and also find a more convenient type of medication that patients could take once a month or so and become pain free.

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-117

Anti-CGRP treatment strategy is one of the alternative therapies to a number of drug treatment options currently available for the prophylaxis and treatment of headache in migraine. Currently, the first choice treatment options of migraine include the use of triptan [serotonin (5-$HT_{1B/D}$)] receptor agonist family drugs and NSAIDs. A number of prophylactic drugs such as the Antiepileptic drugs (AEDs), betablockers, and Ca^{2+} channel blockers are currently being used to treat migraine. These are in addition to some other drugs and non-drug treatment options that are currently available to treat migraine headache. Nevertheless, research in the treatment of migraine is always looking for newer and more convenient, more efficient and more potent drugs or treatment strategies with fewer or no adverse effects.

Although promising, the CGRP-receptor antagonist drugs (the "gepant" family) were discontinued due to their side effects, especially the hepatotoxicity. Several other CGRP receptor antagonists such as MK-3207, BI 44370, BMS-846372 are still in clinical trials, please see[77] for review. Search for newer anti-CGRP compounds with sufficient efficacy and less or no adverse effects continued in recent years.

It seems that blocking CGRP or its receptor alleviates the headache in migraine patients. A number of studies so far in phase one and phase 2, using mAbs against CGRP or its receptors have shown a decrease in the number of headache days per month while did not have a significant adverse effect although these studies are still ongoing at the moment. One important fact about CGRP mAbs is their half-life (and their clearance from the body) which is in the range of a few weeks. This is very good and convenient for migraine patients since with one injection or so per month they experience much less headache days per month although the clearance time of the mAbs from the body is also extended equally.

If proven effective with minimal or no significant adverse events after completing the clinical trials, mAbs against CGRP or its receptors will be another revolution like the triptan family drugs in the field of migraine treatment and will increase our abilities and options to treat migraine effectively. Some of the adverse events of mAbs against CGRP such as infections and abdominal pain seen in some patients may correspond to decrease or inhibition of biological activities of CGRP or activation of some other compensatory mechanisms. Therefore, long term use and monitoring of the patients would add more knowledge to our current understanding.

Such mAbs will certainly be beneficial in other painful or other conditions if their pathophysiology is similar.[130] CGRP is among the four neuropeptides that were increased in the archived neonatal blood of infants who were later (after couple of years) diagnosed having Autism Spectrum Disorders (ASD) or mental retardation.[131]

It is not known why some neuropeptides are increased in ASD, but increased blood serotonin levels has been linked to loss of brain serotoninergic terminals *via* a negative feedback, disrupting the serotonin function leading to a compensatory increase in CGRP level in ASD patients.[132-134] Although, several genes have been implicated in ASD[135] environmental factors including GI abnormalities and immune imbalance might play a role in ASD[136] and other psychological health problems.

The role of CGRP increase in ASD children is not very well known but both serotonin and CGRP are involved here as well. Some GI problems including diarrhea and abdominal pain in autistic children[136-139] are due to various causes but the exact pathomechanism of GI problems in ASD children is not completely understood.[140] It is however possible that anxiety, sensory over-responsivity and GI problems are interrelated phenomena in children with ASD.[141]

Several studies using CGRP knockout mice or other related studies have reported about the various roles of CGRP in pathological conditions in animal studies and results are indicative of some protective and some deleterious effects of CGRP in neuroprotection, immune activation or vascular structure and function.[142-150]

However, mAbs against CGRP in migraine treatment research should tell us more about the long term effect of CGRP inhibition.

Interestingly, inhibiting the TRPV1 receptor or interfering with CGRP activity may improve health and increase age longevity as shown in a recent study in mice[151] and brought the ideas of "die another day"[152] and "a long pain-free life".[153]

Can mAbs against CGRP increase our longevity?

CONFLICTS OF INTEREST

This paper has been written without external financial funding. There is no conflicts of interest.

ACKNOWLEDGMENTS

The author's salary is paid by the University of Central Florida, Orlando, FL, USA.

REFERENCES

1. Weiller C, May A, Limmroth V, et al. Brain stem activation in spontaneous human migraine attacks. *Nat. Med.* 1995; 1: 658-660.

2. Akerman S, Holland PR, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. *Nat Rev Neurosci.* 2011; 12: 570-584. doi: 10.1038/nrn3057

3. Cohen AS, Goadsby PJ. Functional neuroimaging of primary headache disorders. *Expert Rev. Neurother.* 2006; 6: 1159-1171.

doi: 10.1586/14737175.6.8.1159

4. Goadsby PJ. Recent advances in understanding migraine mechanisms, molecules and therapeutics. *Trends Mol. Med.* 2007; 13: 39-44. doi: 10.1016/j.molmed.2006.11.005

5. Samsam M. Central nervous system acting drugs in treatment of migraine headache. *Cent Nerv Syst Agents Med Chem.* 2012; 12(3): 158-172. doi: 10.2174/187152412802430147

6. Lazarov NE. Comparative analysis of the chemical neuroanatomy of the mammalian trigeminal ganglion and mesencephalic trigeminal nucleus. *Prog Neurobiol.* 2002; 66(1): 19-59. doi: 10.1016/S0301-0082(01)00021-1

7. Samsam M, Coveñas R, Ahangari R, Yajeya J. Major neuroanatomical and neurochemical substrates involved in primary headaches. Chapter 1. Neuroanatomy Research Advances; In: Flynn CE, Callaghan BR, eds. Nova Science Publishers; New York; 2009: 1- 58.

8. Samsam M, Coveñas R, Ahangari R, Yajeya J, Narváez JA, Tramu G. Simultaneous depletion of neurokinin A, substance P and calcitonin gene related peptide immunoreactivities in the caudal trigeminal nucleus of the rat following electrical stimulation of the Gasserian ganglion: a possible co-release of neuropeptides. *PAIN.* 2000; 84: 389-395.

9. Friberg L, Olesen J, Olsen TS, Karle A, Ekman R, Fahrenkrug J. Absence of vasoactive peptide release from brain to cerebral circulation during onset of migraine with aura. *Cephalalgia.* 1994; 14(1): 47-54. doi: 10.1046/j.1468-2982.1994.1401047.x

10. Gallai V, Sarchielli P, Floridi A. et al. Vasoactive peptide levels in the plasma of young migraine patients with and without aura assessed both interictally and ictally. *Cephalalgia.* 1995; 15(5): 384-390. doi: 10.1046/j.1468-2982.1995.1505384.x

11. Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. *Cephalalgia.* 2002; 22(1): 54-61. doi: 10.1046/j.1468-2982.2002.00310.x

12. Olesen J, Diener HC, Husstedt IW, et al. BIBN 4096 BS Clinical Proof of Concept Study Group. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. *N Engl J Med.* 2004; 350(11): 1104-1110.

13. Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine-revised report of an EFNS task force. *Eur. J. Neurol.* 2009; 16: 968-981. doi: 10.1111/j.1468-1331.2009.02748.x

14. Humphrey PP. The discovery and development of the triptans, a major therapeutic breakthrough. *Headache.* 2008; 48: 685-687. doi: 10.1111/j.1526-4610.2008.01097.x

15. Bigal ME, Krymchantowski AV, Ho T. Migraine in the triptan era: progresses achieved, lessons learned and future developments. *Arq. Neuropsiquiatr.* 2009; 67: 559-569. doi: 10.1590/S0004-282X2009000300040

16. Ferrari MD, Färkkilä M, Reuter U, European COL-144 Investigators. Acute treatment of migraine with the selective 5-HT1F receptor agonist lasmiditan-a randomised proof-of-concept trial. *Cephalalgia.* 2010; 30: 1170-1178. doi: 10.1177/0333102410375512

17. Samsam M, Coveñas R, Ahangari R, Yajeya J. Neuropeptides and other chemical mediators, and the role of anti-inflammatory drugs in primary headaches. *AIAA-MC.* 2010; 3: 170-188.

18. Amara SG, Jonas V, Rosenfeld MG, Ong ES, Evans RM. Alternative RNA processing in calcitonin gene expression generates mRNAs encoding different polypeptide products. *Nature.* 1982; 298: 240-244. doi: 10.1038/298240a0

19. Brain SD, MacIntyre I, Williams TJ. A second form of human calcitonin gene-related peptide which is a potent vasodilator. *Eur J Pharmacol.* 1986; 124(3): 349-352. doi: 10.1016/0014-2999(86)90238-4

20. Sternini C, Anderson K. Calcitonin gene-related peptide-containing neurons supplying the rat digestive system: differential distribution and expression pattern. *Somatosens Mot Res.* 1992; 9(1): 45-59.

21. Ohno T, Hattori Y, Komine R, et al. Roles of calcitonin gene-related peptide in maintenance of gastric mucosal integrity and in enhancement of ulcer healing and angiogenesis. *Gastroenterology.* 2008; 134(1): 215-225. doi: 10.1053/j.gastro.2007.10.001

22. Durham PL, Vause CV. Calcitonin gene-related peptide (CGRP) receptor antagonists in the treatment of migraine. *CNS Drugs.* 2010; 24(7): 539-548.

23. van Rossum D, Hanisch UK, Quirion R. Neuroanatomical localization, pharmacological characterization and functions of CGRP, related peptides and their receptors. *Neurosci Biobehav Rev.* 1997; 21(5): 649-678.

24. Brain SD, Williams TJ, Tippins JR, Morris HR, MacIntyre I. Calcitonin gene-related peptide is a potent vasodilator. *Nature.* 1985; 313: 54-56.

25. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. *Ann. Neurol.* 2000; 47: 614-624.

26. Villalón CM, Centurión D, Valdivia LF, De Vries P, Saxena PR. An introduction to migraine: from ancient treatment to functional pharmacology and antimigraine therapy. *Proc. West Pharmacol. Soc.* 2002; 45: 199-210.

27. Spierings ELH. Pathogenesis of the migraine attack. *Clin. J. Pain.* 2003; 19: 255-262.

28. Silberstein SD. Migraine pathophysiology and its clinical implications. *Cephalalgia.* 2004: 2: 2-7.

29. Kruuse C, Thomsen L, Birk S, Olesen J. Migraine can be induced by sildenafil without changes in middle cerebral artery diameter. *Brain,* 2003; 126: 241-247.

30. Nichols FT 3rd, Mawad M, Mohr JP, Stein B, Hilal S, Michelsen WJ. Focal headache during balloon inflation in the internal carotid and middle cerebral arteries. *Stroke.* 1990; 21(4): 555-559. doi: 10.1161/01.STR.21.4.555

31. Olesen J, Friberg L, Olsen TS, et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. *Ann Neurol.* 1990; 28(6): 791-798.

32. May A, Büchel C, Turner R, Goadsby PJ. Magnetic resonance angiography in facial and other pain: neurovascular mechanisms of trigeminal sensation. *J Cereb Blood Flow Metab.* 2001; 21(10): 1171-1176. doi: 10.1097/00004647-200110000-00005

33. McLatchie LM, Fraser NJ, Main MJ, et al. RAMPs regulate the transport and ligand specificity of the calcitonin-receptor-like receptor. *Nature.* 1998; 393: 333-339. doi: 10.1038/30666

34. Choksi T, Hay DL, Legon S, et al. Comparison of the expression of calcitonin receptor-like receptor (CRLR) and receptor activity modifying proteins (RAMPs) with CGRP and adrenomedullin binding in cell lines. *Br J Pharmacol*. 2002; 136(5): 784-792. doi: 10.1038/sj.bjp.0704761

35. Poyner DR, Sexton PM, Marshall I, et al. International Union of Pharmacology. XXXII. The mammalian calcitonin gene-related peptides, adrenomedullin, amylin, and calcitonin receptors. *Pharmacol Rev.* 2002; 54(2): 233-246.

36. Miller PS, Barwell J, Poyner DR, Wigglesworth MJ, Garland SL, Donnelly D. Non-peptidic antagonists of the CGRP receptor, BIBN4096BS and MK-0974, interact with the calcitonin receptor-like receptor via methionine-42 and RAMP1 via tryptophan-74. *Biochem. Biophys. Res. Commun.* 2010; 391: 437-442. doi: 10.1016/j.bbrc.2009.11.076

37. Mallee JJ, Salvatore CA, LeBourdelles B, et al. Receptor activity-modifying protein 1 determines the species selectivity of non-peptide CGRP receptor antagonists. *J Biol Chem.* 2002; 277(16): 14294-14298. doi: 10.1074/jbc.M109661200

38. Zhang Z, Winborn CS, Marquez de Prado B, Russo AF. Sensitization of calcitonin gene-related peptide receptors by receptor activity-modifying protein-1 in the trigeminal ganglion. *J. Neurosci.,* 2007; 27: 2693-2703.

39. Hay DL, Howitt SG, Conner AC, Doods H, Schindler M, Poyner DR. A comparison of the actions of BIBN4096BS and CGRP(8-37) on CGRP and adrenomedullin receptors expressed on SK-N-MC, L6, Col 29 and Rat 2 cells. *Br J Pharmacol.* 2002; 137(1): 80-86.

40. Dennis T, Fournier A, Cadieux A, et al. hCGRP8-37, a calcitonin gene-related peptide antagonist revealing calcitonin gene-related peptide receptor heterogeneity in brain and periphery. *J. Pharmacol. Exp. Ther.* 1990; 254: 123-128.

41. Hay DL, Poyner DR, Quirion R, et al. International Union of Pharmacology. International Union of Pharmacology. LXIX. Status of the calcitonin gene-related peptide subtype 2 receptor. *Pharmacol. Rev.* 2008; 60: 143-145. doi: 10.1124/pr.108.00372

42. Kitazono T, Heistad DD, Faraci FM. Role of ATP-sensitive K+ channels in CGRP-induced dilatation of basilar artery in vivo. *Am J Physiol.* 1993; 265(2 Pt 2): H581-H585.

43. Hong KW, Yoo SE, Yu SS, Lee JY, Rhim BY. Pharmacological coupling and functional role for CGRP receptors in the vasodilation of rat pial arterioles. *Am J Physiol.* 1996; 270(1 Pt 2): H317-H323.

44. Birk S, Kruuse C, Petersen KA, Tfelt-Hansen P, Olesen J. The headache-inducing effect of cilostazol in human volunteers. *Cephalalgia.* 2006; 26(11): 1304-1309. doi: 10.1111/j.1468-2982.2006.01218.x

45. Bellamy J, Bowen EJ, Russo AF, Durham PL. Nitric oxide regulation of calcitonin gene-related peptide gene expression in rat trigeminal ganglia neurons. *Eur J Neurosci.* 2006; 23(8): 2057-2066. doi: 10.1111/j.1460-9568.2006.04742.x

46. Eftekhari S, Gaspar RC, Roberts R, et al. Localization of CGRP receptor components and receptor binding sites in rhesus monkey brainstem: a detailed study using in situ hybridization, immunofluorescence and autoradiography. *J Comp Neurol*. 2015. doi: 10.1002/cne.23828

47. Edvinsson L, Eftekhari S, Salvatore CA, Warfvinge K. Cerebellar distribution of calcitonin gene-related peptide (CGRP) and its receptor components calcitonin receptor-like receptor (CLR) and receptor activity modifying protein 1 (RAMP1) in rat. *Mol Cell Neurosci.* 2011; 46(1): 333-339. doi: 10.1016/j.mcn.2010.10.005

48. Ottosson A, Edvinsson L. Release of histamine from dural mast cells by substance P and calcitonin gene-related peptide. *Cephalalgia.* 1997; 17(3): 166-174. doi: 10.1046/j.1468-2982.1997.1703166.x

49. Lennerz JK, Rühle V, Ceppa EP, et al. Calcitonin receptor-like receptor (CLR), receptor activity-modifying protein 1 (RAMP1), and calcitonin gene-related peptide (CGRP) immunoreactivity in the rat trigeminovascular system: differences between peripheral and central CGRP receptor distribution. *J Comp Neurol.* 2008; 507(3): 1277-1299. doi: 10.1002/cne.21607

50. Yu LC, Zheng EM, Lundeberg T. Calcitonin gene-related peptide 8-37 inhibits the evoked discharge frequency of wide dynamic range neurons in dorsal horn of the spinal cord in rats. *Regul Pept.* 1999; 83(1): 21-24. doi: 10.1016/S0167-0115(99)00046-4

51. Benemei S, De Cesaris F, Fusi C, Rossi E, Lupi C, Geppetti P. TRPA1 and other TRP channels in migraine. *J Headache Pain.* 2013; 14: 71.

52. Reddington M, Priller J, Treichel J, Haas C, Kreutzberg GW. Astrocytes and microglia as potential targets for calcitonin gene related peptide in the central nervous system. *Can J Physiol Pharmacol.* 1995; 73(7): 1047-1049.

53. Arulmani U, Gupta S, Massen Van Den Brink AM, Centurión D, Villalón CM, Saxena PR. Experimental migraine models and their relevance in migraine therapy. *Cephalalgia,* 2006; 26: 642-659. doi: 10.1111/j.1468-2982.2005.01082.x

54. Linde M. Migraine: a review and future directions for treatment. *Acta Neurol. Scand.,* 2006; 114: 71-83. doi: 10.1111/j.1600-0404.2006.00670.x

55. Edvinsson L, Alm R, Shaw D, et al. Effect of the CGRP receptor antagonist BIBN4096BS in human cerebral, coronary and omental arteries and in SK-N-MC cells. *Eur J Pharmacol.* 2002; 434: 49-53. doi: 10.1016/S0014-2999(01)01532-1

56. Jansen-Olesen I, Jorgensen L, Engel U, Edvinsson L. In-depth characterization of CGRP receptors in human intracranial arteries. *Eur. J. Pharmacol.,* 2003; 481: 207-216. doi: 10.1016/j.ejphar.2003.09.021

57. Wu D, Eberlein W, Rudolf K, Engel W, Hallermayer G, Doods H. Characterisation of calcitonin gene-related peptide receptors in rat atrium and vas deferens: evidence for a [Cys(Et)(2,7)]hCGRP-preferring receptor. *Eur. J. Pharmacol.* 2000; 400: 313-319. doi: 10.1016/S0014-2999(00)00407-6

58. Jansen-Olesen I, Kaarill L, Edvinsson L. Characterization of CGRP(1) receptors in the guinea pig basilar artery. *Eur. J. Pharmacol.* 2001; 414: 249-258. doi: 10.1016/S0014-2999(01)00760-9

59. Wu D, Doods H, Arndt K, Schindler M. Development and potential of non-peptide antagonists for calcitonin-gene-related peptide (CGRP) receptors: evidence for CGRP receptor heterogeneity. *Biochem Soc Trans.* 2002; 30: 468-473. doi: 10.1042/bst0300468

60. Gupta S, Akerman S, van den Maagdenberg AM, Saxena PR, Goadsby PJ, van den Brink AM. Intravital microscopy on a closed cranial window in mice: a model to study trigeminovascular mechanisms involved in migraine. *Cephalalgia.* 2006, 26, 1294-303.

61. Petersen KA, Birk S, Lassen LH, et al. The CGRP-antagonist, BIBN4096BS does not affect cerebral or systemic haemodynamics in healthy volunteers. *Cephalalgia.* 2005; 25: 139-147. doi: 10.1111/j.1468-2982.2004.00830.x

62. Tröltzsch M, Denekas T, Messlinger K. The calcitonin gene-related peptide (CGRP) receptor antagonist BIBN4096BS reduces neurogenic increases in dural blood flow. *Eur J Pharmacol.* 2007; 562: 103-110. doi: 10.1016/j.ejphar.2007.01.058

63. Gupta S, Mehrotra S, Villalon CM, et al. Characterisation of CGRP receptors in human and porcine isolated coronary arteries: evidence for CGRP receptor heterogeneity. *Eur J Pharmacol.* 2006; 530: 107-116. doi: 10.1016/j.ejphar.2005.11.020

64. Hasbak P, Saetrum Opgaard O, Eskesen K, et al. Investigation of CGRP receptors and peptide pharmacology in human coronary arteries. Characterization with a nonpeptide antagonist. *J. Pharmacol. Exp. Ther.* 2003; 304: 326-333. doi: 10.1124/jpet.102.037754

65. Sixt ML, Messlinger K, Fischer MJ. Calcitonin gene-related peptide receptor antagonist olcegepant acts in the spinal trigeminal nucleus. *Brain.* 2009; 132: 3134-3141. doi: 10.1093/brain/awp168

66. Ho TW, Mannix LK, Fan X, et al. MK-0974 Protocol 004 study group. Collaborators (20), Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine. *Neurology.* 2008; 70: 1304-1312.

67. Connor K.M, Shapiro RE, Diener HC, et al. Randomized, controlled trial of telcagepant for the acute treatment of migraine. *Neurology.* 2009; 73: 970-977. doi: 10.1212/WNL.0b013e3181b87942

68. Iovino M, Feifel U, Yong CL, Wolters JM, Wallenstein G. Safety, tolerability and pharmacokinetics of BIBN 4096 BS, the first selective small molecule calcitonin gene-related peptide receptor antagonist, following single intravenous administration in healthy volunteers. *Cephalalgia.* 2004; 24: 645-656. doi:

10.1111/j.1468-2982.2004.00726.x

69. Ho TW, Ferrari MD, Dodick DW, et al. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. *Lancet.* 2008, 372: 2115-2123. doi: 10.1016/S0140-6736(08)61626-8

70. Summ O, Charbit AR, Andreou AP, Goadsby PJ. Modulation of nocioceptive transmission with calcitonin gene-related peptide receptor antagonists in the thalamus. *Brain.* 2010; 133(9): 2540-2548. doi: 10.1093/brain/awq224

71. Tepper SJ, Cleves C. Telcagepant, a calcitonin gene-related peptide antagonist for the treatment of migraine. *Curr. Opin. Investig. Drugs.* 2009; 10: 711-720.

72. Tfelt-Hansen P, Olesen J. Possible site of action of CGRP antagonists in migraine. *Cephalalgia.* 2011; 31: 748-750. doi: 10.1177/0333102411398403

73. Diener HC, Barbanti P, Dahlöf C, Reuter U, Habeck J, Podhorna J. BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. *Cephalalgia.* 2011; 31(5): 573-584. doi: 10.1177/0333102410388435

74. Benemei S, Nicoletti P, Capone JA, Geppetti P. Pain pharmacology in migraine: focus on CGRP and CGRP receptors. *Neurol. Sci.,* 2007, 28(Suppl 2): S89-S93. doi: 10.1007/s10072-007-0757-5

75. Villalón CM, Olesen J. The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute antimigraine drugs. *Pharmacol. Ther.,* 2009; 124: 309-323. doi: 10.1016/j.pharmthera.2009.09.003

76. Karsan N, Goadsby PJ. Calcitonin gene-related peptide and migraine. *Curr Opin Neurol.* 2015; 28(3): 250-254.

77. Karsan N, Goadsby PJ. CGRP mechanism antagonists and migraine management. *Curr Neurol Neurosci Rep.* 2015; 15(5): 25.

78. Hougaard A, Tfelt-Hansen P. Review of dose-response curves for acute antimigraine drugs: triptans, 5-HT1F agonists and CGRP antagonists. *Expert Opin Drug Metab Toxicol.* 2015; 22: 1-10.

79. Hoffmann J, Goadsby PJ. New agents for acute treatment of migraine: CGRP receptor antagonists, iNOS Inhibitors. *Curr Treat Options Neurol.* 2012; 14(1): 50-59. doi: 10.1007/s11940-011-0155-4

80. Tajti J, Csáti A, Vécsei L. Novel strategies for the treatment of migraine attacks via the CGRP, serotonin, dopamine, PAC1, and NMDA receptors. *Expert Opin Drug Metab Toxicol.* 2014; 10(11): 1509-1520.

81. Edvinsson L. CGRP receptor antagonists and antibodies against CGRP and its receptor in migraine treatment. *Br J Clin Pharmacol.* 2015; 80(2): 193-199. doi: 10.1111/bcp.12618

82. Bigal ME, Walter S, Rapoport AM. Therapeutic antibodies against CGRP or its receptor. *Br J Clin Pharmacol.* 2015; 79(6): 886-895. doi: 10.1111/bcp.12591

83. Bigal ME, Walter S. Monoclonal antibodies for migraine: preventing calcitonin gene-related peptide activity. *CNS Drugs.* 2014; 28(5): 389-399. doi: 10.1007/s40263-014-0156-4

84. Reuter U. Anti-CGRP antibodies: a new approach to migraine prevention. *Lancet Neurol.* 2014; 13(9): 857-859. doi: 10.1016/S1474-4422(14)70126-7

85. Burton DR. Antibodies, viruses and vaccines. *Nat Rev Immunol.* 2002; 2(9): 706-713. doi: 10.1038/nri891

86. Nimmerjahn F, Gordan S, Lux A. FcγR dependent mechanisms of cytotoxic, agonistic, and neutralizing antibody activities. *Trends Immunol.* 2015; 36(6): 325-336.

87. Bigal ME, Walter S, Rapoport AM. Calcitonin gene-related peptide (CGRP) and migraine current understanding and state of development. *Headache.* 2013; 53(8): 1230-1244. doi: 10.1111/head.12179

88. Alder Biopharmaceuticals, Inc. A parallel group, double-blind, randomized, placebo controlled dose-ranging phase 2 trial to evaluate the efficacy, safety, and pharmacokinetics of ALD403 administered intravenously in patients with chronic migraine. http://www.alderbio.com/clinical-trials/ 2013; Accessed August, 2015.

89. Alder Biopharmaceuticals, Inc. Safety tolerability and pharmacokinetics of ALD403. Available at: https://clinicaltrials.gov/ct2/show/NCT01579383?term=ALD403&rank=1 2013; Accessed August, 2015.

90. Alder Biopharmaceuticals, Inc. Safety, efficacy and pharmacokinetics of ALD403. Available at: https://clinicaltrials.gov/ct2/show/NCT01772524?term=ALD403&rank=3 2014; Accessed August, 2015.

91. Alder Biopharmaceuticals, Inc. A multicenter assessment of ALD403 in chronic migraine. https://clinicaltrials.gov/ct2/show/NCT02275117?term=ALD403&rank=2 2015; Accessed August, 2015.

92. Dodick DW, Goadsby PJ, Silberstein SD, et al. 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; 13(11): 1100-1107. doi: 10.1016/S1474-4422(14)70209-1

93. Eli Lilly and Company. CGRP mAb migraine prevention. Available at: http://www.lilly.com/SiteCollectionDocuments/Pipeline/Clinical%20Development%20Pipeline/10.html. Accessed in Aug 2015.

94. 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; 13(9): 885-892. doi: 10.1016/S1474-4422(14)70128-0

95. Eli Lilly and Company. A study of LY2951742 in healthy Japanese and Caucasian participants. Available at: https://clinicaltrials.gov/ct2/show/NCT02104765?term=LY2951742&rank=2 2015; Accessed August, 2015.

96. Eli Lilly and Compan. A study of LY2951742 in healthy volunteers. Available at: https://clinicaltrials.gov/ct2/show/NCT01337596?term=LY2951742&rank=5 2015; Accessed August, 2015.

97. Eli Lilly and Company. A study of LY2951742 in participants with migraine. Available at: https://clinicaltrials.gov/ct2/show/NCT01625988?term=LY2951742&rank=7 2015; Accessed August, 2015.

98. Vermeersch S, Benschop RJ, Van Hecken A, et al. Translational pharmacodynamics of CGRP monoclonal antibody LY2951742 in a capsaicin-induced dermal blood flow model. *J Pharmacol Exp Ther.* 2015; 354(3): 350-357.

99. Eli Lilly and Company. A Study of LY2951742 in Participants With Chronic Cluster Headache. Available at: https://clinicaltrials.gov/ct2/show/NCT02438826?term=LY2951742&rank=3 2015; Accessed August, 2015.

100. Teva to Present New Findings at the American Headache Society (AHS) Meeting – Analysis of Migraine Phase IIb Studies Provides Novel Insights into TEV-48125 Efficacy and Safety in Both Episodic & Chronic Migraine. Available at: http://news.tevausa.com/mobile.view?c=251945&v=203&d=1&id=2060482, 2015.

101. Schuster NM, Vollbracht S, Rapoport AM. Emerging treatments for the primary headache disorders. *Neurol Sci.* 2015; 36(Suppl 1): 109-113.

102. Walter S, Bigal ME. TEV-48125: a review of a monoclonal CGRP antibody in development for the preventive treatment of migraine. *Curr Pain Headache Rep.* 2015; 19(3): 6.

103. Walter S, Alibhoy A, Escandon R, Bigal ME. Evaluation of cardiovascular parameters in cynomolgus monkeys following IV administration of LBR-101, a monoclonal antibody against calcitonin gene-related peptide. *MAbs.* 2014; 6(4): 871-878.

104. Bigal ME, Escandon R, Bronson M, et al. Safety and tolerability of LBR-101, a humanized monoclonal antibody that blocks the binding of CGRP to its receptor: Results of the Phase 1 program. *Cephalalgia.* 2013; 34(7): 483-492.

105. TEVA latest news. Available at: http://www.tevapharm.com/news/?itemid=%7B007EDCEC-98E8-41EA-8775-2F4E78BB12E6%7D 2015; Accessed 2015.

106. Amgen. Amgen To Present AMG 334 Data At 17th Congress of the International Headache Society: Data Evaluating Safety and Efficacy of AMG 334 Provides New Insights Into Preventive Treatment of Migraine. Available at: http://wwwext.amgen.com/media/media_pr_detail.jsp?year=2015&releaseID=2046668. Accessed August, 2015.

107. Amgen. Ascending single doses of AMG 334 in healthy subjects and migraine patients. Available at: https://clinicaltrials.gov/ct2/show/NCT01688739?term=AMG+334&rank=1 2014; Accessed August, 2015.

108. Amgen. Ascending multiple-doses of AMG 334 in healthy subjects and in Migraine Patients. Available at: https://clinicaltrials.gov/ct2/show/NCT01723514?term=AMG+334&rank=3 2013; Accessed August, 2015.

109. Amgen. Ascending multiple-doses of AMG 334 in healthy subjects and in migraine patients. Available at: http://www.amgentrials.com/amgen/trialsummary.aspx?studyid=20101268. Accessed August, 2015.

110. Amgen. A phase 2 study to evaluate the efficacy and safety of AMG 334 in migraine prevention. Available at: https://clinicaltrials.gov/ct2/show/NCT01952574?term=AMG+334&rank=2 2015; Accessed August, 2015.

111. Amgen. A sudy to evaluate the efficacy and safety of AMG 334 in chronic migraine prevention. Available at: http://www.amgentrials.com/amgen/trialsummary.aspx?studyid=20120295 2015; Accessed August, 2015.

112. Amgen. A study to assess the long-term safety and efficacy of AMG 334 in chronic migraine prevention. Available at: http://www.amgentrials.com/amgen/trialsummary.aspx?studyid=20130255 2015; Accessed August, 2015.

113. Amgen. Amgen Presents Open-Label Extension Data From

Ongoing Phase 2 Study Of AMG 334 In The Prevention Of Episodic Migraine. Available at: http://wwwext.amgen.com/media/media_pr_detail.jsp?year=2015&releaseID=2061044 2015; Accessed September, 2015.

114. PRNewswire/THOUSAND OAKS, Calif. Amgen presents first phase 2 data for AMG 334 in the Prevention of Episodic Migraine. Available at: http://www.prnewswire.com/news-releases/amgen-presents-first-phase-2-data-for-amg-334-in-the-prevention-of-episodic-migraine-300084005.html 2015; Accessed May 15, 2015.

115. PRNewswire/ THOUSAND OAKS, Calif. Amgen Presents open-label extension data from ongoing phase 2 study of amg 334 in the prevention of episodic migraine: Available at: http://wwwext.amgen.com/media/media_pr_detail.jsp?year=2015&releaseID=2061044 2015; Accessed June 19, 2015.

116. Nohr D, Weihe E. The neuroimmune link in the bronchus-associated lymphoid tissue (BALT) of cat and rat: peptides and neural markers. *Brain Behav Immun.* 1991; 5(1): 84-101.

117. Keith IM. The role of endogenous lung neuropeptides in regulation of the pulmonary circulation. *Physiol Res.* 2000; 49(5): 519-537.

118. Dakhama A, Larsen GL, Gelfand EW. Calcitonin gene-related peptide: role in airway homeostasis. *Curr Opin Pharmacol*. 2004; 4(3): 215-220.

119. Okajima K, Harada N. Regulation of inflammatory responses by sensory neurons: molecular mechanism(s) and possible therapeutic applications. *Curr Med Chem.* 2006; 13(19): 2241-2251.

120. Springer J, Geppetti P, Fischer A, Groneberg DA. Calcitonin gene-related peptide as inflammatory mediator. *Pulm Pharmacol Ther.* 2003; 16(3): 121-130.

121. Holzmann B. Antiinflammatory activities of CGRP modulating innate immune responses in health and disease. *Curr Protein Pept Sci.* 2013; 14(4): 268-274.

122. Alpaerts K, Buckinx R, Adriaensen D, Van Nassauw L, Timmermans JP. Identification and putative roles of distinct subtypes of intestinal dendritic cells in neuroimmune communication: what can be learned from other organ systems? *Anat Rec (Hoboken).* 2015; 298(5): 903-916. doi: 10.1002/ar.23106

123. Assas BM, Miyan JA, Pennock JL. Cross-talk between neural and immune receptors provides a potential mechanism of homeostatic regulation in the gut mucosa. *Mucosal Immunol.* 2014; 7(6): 1283-1289. doi: 10.1038/mi.2014.80

124. Evangelista S. Capsaicin receptor as target of calcitonin gene-related peptide in the gut. *Prog Drug Res.* 2014; 68: 259-276. doi: 10.1007/978-3-0348-0828-6_10

125. Taché Y, Garrick T, Raybould H. Central nervous system action of peptides to influence gastrointestinal motor function. *Gastroenterology.* 1990; 98(2): 517-528.

126. Demir IE, Schäfer KH, Tieftrunk E, Friess H, Ceyhan GO. Neural plasticity in the gastrointestinal tract: chronic inflammation, neurotrophic signals, and hypersensitivity. *Acta Neuropathol.* 2013; 125(4): 491-509. doi: 10.1007/s00401-013-1099-4

127. Gaete PS, Lillo MA, Figueroa XF. Functional role of connexins and pannexins in the interaction between vascular and nervous system. *J Cell Physiol.* 2014; 229(10): 1336-1345. doi: 10.1002/jcp.24563

128. Reuss S. Trigeminal innervation of the mammalian pineal gland. *Microsc Res Tech.* 1999; 46(4-5): 305-309. doi: 10.1002/(SICI)1097-0029(19990815/01)46:4/5<305::AID-JEMT7>3.0.CO;2-#

129. Vega AV, Avila G. CGRP, a vasodilator neuropeptide that stimulates neuromuscular transmission and EC coupling. *Curr Vasc Pharmacol.* 2010; 8(3): 394-403. doi: 10.2174/157016110791112287

130. Ishida K, Kawamata T, Tanaka S, Shindo T, Kawamata M. Calcitonin gene-related peptide is involved in inflammatory pain but not in postoperative pain. *Anesthesiology.* 2014; 121(5): 1068-1079. doi: 10.1097/ALN.0000000000000364

131. Nelson KB, Grether JK, Croen LA, et al. Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation. *Ann Neurol.* 2001; 49: 597-606.

132. McNamara IM, Borella AW, Bialowas LA, Whitaker-Azmitia PM. Further studies in the developmental hyperserotonemia model (DHS) of autism: social, behavioral and peptide changes. *Brain Res.* 2008; 1189: 203-214.

133. Gabriele S, Sacco R, Persico AM. Blood serotonin levels in autism spectrum disorder: a systematic review and meta-analysis. *Eur Neuropsychopharmacol.* 2014; 24(6): 919-929. doi: 10.1016/j.euroneuro.2014.02.004

134. Yang CJ, Tan HP, Du YJ. The developmental disruptions of serotonin signaling may involved in autism during early brain development. *Neuroscience.* 2014; 267: 1-10. doi: 10.1016/j.neuroscience.2014.02.021

135. Miles JH. Autism spectrum disorders--a genetics review. *Genet Med.* 2011; 13(4): 278-294. doi: 10.1097/GIM.0b013e3181ff67ba

136. Samsam M, Ahangari R, Naser SA. Pathophysiology of au-

tism spectrum disorders: revisiting gastrointestinal involvement and immune imbalance. *World J Gastroenterol.* 2014; 20(29): 9942-9951. doi: 10.3748/wjg.v20.i29.9942

137. White JF. Intestinal pathophysiology in autism. *Exp Biol Med (Maywood).* 2003; 228: 639-649.

138. Chaidez V, Hansen RL, Hertz-Picciotto I. Gastrointestinal problems in children with autism, developmental delays or typical development. *J Autism Dev Disord.* 2014; 44(5): 1117-1127. doi: 10.1007/s10803-013-1973-x

139. Mazefsky CA, Schreiber DR, Olino TM, Minshew NJ. The association between emotional and behavioral problems and gastrointestinal symptoms among children with high-functioning autism. *Autism.* 2014; 18(5): 493-501. doi: 10.1177/1362361313485164

140. Buie T, Campbell DB, Fuchs GJ 3rd, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics.* 2010; 125(Suppl 1): S1-S18. doi: 10.1542/peds.2009-1878C

141. Mazurek MO, Vasa RA, Kalb LG, et al. Anxiety, sensory over-responsivity, and gastrointestinal problems in children with autism spectrum disorders. *J Abnorm Child Psychol.* 2013; 41(1): 165-176. doi: 10.1007/s10802-012-9668-x

142. Mikami N, Watanabe K, Hashimoto N, et al. Calcitonin gene-related peptide enhances experimental autoimmune encephalomyelitis by promoting Th17-cell functions. *Int Immunol.* 2012; 24(11): 681-691. doi: 10.1093/intimm/dxs075

143. Jusek G, Reim D, Tsujikawa K, Holzmann B. Deficiency of the CGRP receptor component RAMP1 attenuates immunosuppression during the early phase of septic peritonitis. *Immunobiology.* 2012; 217(8): 761-767. doi: 10.1016/j.imbio.2012.04.009

144. Park SH, Sim YB, Kim CH, Lee JK, Lee JH, Suh HW. Role of α-CGRP in the regulation of neurotoxic responses induced by kainic acid in mice. *Peptides*. 2013; 44: 158-162. doi: 10.1016/j.peptides.2013.04.001

145. Sardi C, Zambusi L, Finardi A, et al. Involvement of calcitonin gene-related peptide and receptor component protein in experimental autoimmune encephalomyelitis. *J Neuroimmunol.* 2014; 271(1-2): 18-29. doi: 10.1016/j.jneuroim.2014.03.008

146. Engel MA, Khalil M, Siklosi N, et al. Opposite effects of substance P and calcitonin gene-related peptide in oxazolone colitis. *Dig Liver Dis.* 2012; 44(1): 24-29. doi: 10.1016/j.dld.2011.08.030

147. Yang L, Sakurai T, Kamiyoshi A, et al. Endogenous CGRP protects against neointimal hyperplasia following wire-induced vascular injury. *J Mol Cell Cardiol.* 2013; 59: 55-66. doi: 10.1016/j.yjmcc.2013.02.002

148. Li J, Carnevale KA, Dipette DJ, Supowit SC. Renal protective effects of α-calcitonin gene-related peptide in deoxycorticosterone-salt hypertension. *Am J Physiol Renal Physiol.* 2013; 304(7): F1000-F1008. doi: 10.1152/ajprenal.00434.2012

149. Mai TH, Wu J, Diedrich A, Garland EM, Robertson D. Calcitonin gene-related peptide (CGRP) in autonomic cardiovascular regulation and vascular structure. *J Am Soc Hypertens.* 2014; 8(5): 286-296. doi: 10.1016/j.jash.2014.03.001

150. Smillie SJ, King R, Kodji X, et al. An ongoing role of α-calcitonin gene-related peptide as part of a protective network against hypertension, vascular hypertrophy, and oxidative stress. *Hypertension.* 2014; 63(5): 1056-1062. doi: 10.1161/HYPERTENSIONAHA.113.02517

151. Riera CE, Huising MO, Follett P, et al. TRPV1 pain receptors regulate longevity and metabolism by neuropeptide signaling. *Cell.* 2014; 157(5): 1023-1036. doi: 10.1016/j.cell.2014.03.051

152. Steculorum SM, Brüning JC. Die another day: a painless path to longevity. *Cell.* 2014; 157(5): 1004-1006. doi: 10.1016/j.cell.2014.05.013

153. Bray N. Neuroendocrinology: a long pain-free life. *Nat Rev Drug Discov.* 2014; 13(7): 495. doi: 10.1038/nrn3778