INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Review Article

ROLE OF CALCITONIN GENE RELATED PEPTIDE IN DEVELOPMENT OF mAB IN MIGRAINE: A REVIEW

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Article Received on: 05/09/18 Approved for publication: 22/11/18

DOI: 10.7897/2230-8407.0912285

ABSTRACT

Migraine which was once believed to be caused by change in vascular activity in early twentieth century resulting from transient vasoconstriction in migraine aura and headache from rebound vasodilation is replaced with neurovascular phenomenon, predominantly neurovascular which is evoked by release of calcitonin gene-related peptide (CGRP), a vasoactive neuropeptide reported to be present in cranial nuclei from trigeminal sensory nerves. An elevated level of calcitonin gene-related peptide (CGRP) dilates the intracranial and extracranial blood vessels and regulates vascular nociception is a likely mechanism in migraine pathology. It is advocated that calcitonin gene-related peptide (CGRP) plays a profound role in pathophysiology of migraine. Monoclonal antibodies with promising safety and efficacy are advocated as prophylactic treatment for episodic and chronic migraine which targets against CGRP or CGRP receptor based on results obtained from phase II and III clinical trials.

Key words: migraine, calcitonin gene-related peptide (CGRP), CGRP receptors, Anti-CGRP Monoclonal Antibodies, Clinical trials.

INTRODUCTION

Migraine is highly prevalent and complex, neurovascular disorder and is generally inherited with recurrent, severe headache that interferes with normal functioning of the brain, characterized by recurring episodes of throbbing headache. Migraine effects approximately 1 in 10 people globally. Migraine pain are diagnosed as episodic, however, few experiences chronic migraine associated with nausea, vomiting, photosensitivity, irritability, sensitivity to loud sounds and or strong smell with autonomic, cognitive and motor interference [1]. Certain triggers provoke migraine attack as such stress, excessive or insufficient sleep, hormones, food additives like aspartame and monosodium glutamate, hunger and dehydration, immoderate caffeine consumption, over exposure to medicine specifically analgesics, alcohol, strong odor, intense sound, pulsating lights [2].

According to World Health organization (WHO) migraine is one of the common causes of headache globally causing burden to the people extensively effecting people of all ages, it is more prominent in female then in male with prevalence of 11.4% (7.9% males and 14.8% females) worldwide [3].

The debate over the pathophysiology of migraine was largely centered on neural or vascular mechanisms that may be involved in triggering migraine attacks. Vascular theory was discovered by Galen in second century and Thomas Willis in 17th century re-proposed the vascular concept [7]. However, in early 1940's Harold Wolff demonstrated that severity of migraine was associated with external carotid arteries and decrease in throbbing frequency reduced headache intensity. Several studies showed induction of vasoconstriction of temporal and meningeal arteries resulted in relieve from throbbing headache. Intracranial and extracranial arteries have nociceptive role in migraine and can potentially innervated by trigeminal nerve [10]. Dilation of meningeal and cerebral vessel was observed during migraine in one of the studies [8]. Wider superficial Temporal arteries (extracranial arteries), was seen on painful side of the head and constriction of the artery relieved the pain. However, recent studies conclude that the dilation of extracranial arteries was not related with migraine pain yet there was insignificant dilation on intracranial vessel [9].

The origin of the neuronal mechanisms that underlie that migraine involves activation and sensitization of trigeminovascular pathways, as well as brain stem and diencephalic nuclei, although a complete pathophysiologic mechanism of migraine headache is not known [1]. Several studies revealed migraine is associated with release of vasoactive peptides such as; Calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP-38) and neurotransmitter nitric oxide (NO) all of which act as a potent vasodilator and are implicated in migraine pathophysiology. Migraine occurs when certain triggers provoke neural dysfunction within brain causes meningeal vasodilation and activation of trigeminal system resulting in release of neuropeptides particularly calcitonin gene-related peptide (CGRP), a potent vasodilator which induce neurogenic inflammation and aggravate vasodilation where the pain is transmitted to trigeminal nerve and the pain stimulus is carried through trigeminal tract in caudal brainstem, pain signals are then relayed to thalamus and ascends to higher cervical cord via Aδ and C-afferent nerve fibers [4,5,6].

Calcitonin Gene Related Peptide

CGRP belongs to calcitonin gene peptide family along with another peptides amylin and adrenomedullin [11] with a half-life (t1/2) of 10 minutes. It consists of 37 amino acid neuropeptide results from alternative splicing of RNA transcript of calcitonin/ CGRP gene located on chromosome 11 available in two isoforms α -CGRP and β -CGRP [12,13], where α-CGRP is extensively found in primary spinal afferents from sensory ganglia, whereas β-CGRP is found abundantly in the enteric nervous system [14]. β -isoform differs from a-isoform by 3 amino acids. Immunoreactive neuron account for up to 50% of all neuron in trigeminal ganglia [15]. In-situ hybridization technique shows that 40% of cell bodies

contains CGRP mRNA and CGRP [16,17]. CGRP level within extracranial blood vessel increase as well as in saliva with trigeminal ganglion stimulation [18]. It can be demonstrated by intravenous admiration of CGRP that induce migraine attack in migraineurs [19].

CGRP is predominantly expressed in Aδ and C nerve fibers which transmit pain signals to central nervous system [20]. CGRP is associated with neurogenic inflammation and meningeal vasodilation and degranulation of mast cells within intracranial vasculature which results in peripheral sensitization of trigeminal system [21,22] all these processes are involved in painful episodes of migraine [23]. Subsequently CGRP would protrude to the trigeminal nucleus caudalis after trigeminal activation to excite second order neuron and glial cells in initiation and maintenance of persistent pain. Release of CGRP during neuronal activation of cranial ganglia stimulate satellite glial cells which release pro-inflammatory cytokines, which further modulate neuronal response [24,25,26].

Calcitonin Gene Related Peptide Receptors

CGRP receptors include; calcitonin like receptor (CLR), receptor activity modifying protein 1(RAMP1), receptor component protein (RCP) [27] belongs to secretin family of G-protein couple receptor [28]. RAMP1 transfer of CLR to surface of cell membrane [29]. CGRP receptors are expressed in heart, pancreas, dura matter, peripheral and central nervous system and also in trigeminal ganglion neuron and satellite glial cell [30,31]. 37% of neuron is expressed with CLR and 36% with RAMP1 in human trigeminal ganglia (TRIG) [32].

Anti-CGRP Monoclonal Antibodies

Anti-CGRP monoclonal antibodies changed the treatment paradigm for migraine, for preventing CGRP induced trigeminal nociceptive transmission to reduce frequency of headache in chronic migraine. It is seen that monthly migraine days was reduced by 50% and eliminated migraines in 10% to 20% of patients. The onset of prophylaxis appears to be within days instead of months [33]. Four monoclonal antibodies, eptinezumab (ALD403), erenumab (AMG-334), fremanezumab (TEV-48215), galcanezumab (LY2951742) have been approved for the treatment of episodic and chronic migraine, which have met the clinical trial end point. They show high efficacy with tolerable adverse effect. Monoclonal antibodies have distinctive pharmacological features that makes them highly safe and effective such as; large molecular size, extended half-life (T ½), slow distribution and target specificity, impermeable to blood brain barrier, low drug-drug interactions. Due to high molecular size it shows low permeability to cell membrane therefore administered parentally hence given as prophylactic treatment in a disposable auto injector form, once a month or quarterly [34,35,36].

Three humanized antibodies namely, eptinezumab, fremanezumab and galcanezumab act against CGRP release and erenumab target CGRP receptor [37]. Galcanezumab displayed lesser potency against CGRP with rapid target binding and dissociation [38]. Unlike galcanezumab, eptinezumab and fremanezumab showed slow dissociation and prolong action [38,39]. Epitinezumab inactivated CGRP twice as rapidly as fremanezumab [38].

Erenumab is the only mAB that compete with CGRP to bind to CGRP receptor (RAMP1-CLR) reversibly with high affinity. It broadly occupies the ligand-binding site of receptor and block effectively [39,40].

AUTHOR'S NOTE

Highlights of information on developmental pathway of monoclonal antibodies in Phase II and Phase III Clinical trials which was summarized in Table. 1 [41,42] from selected materials. The information given is meant to provide assess the development status of a new drug and should not be used in making patient care decisions.

These data highlight the safety, tolerance, and efficacy of these medications in the prevention of recurrent migraine attacks (the results of phase 2 clinical trials are summarized in Table 2 and Table 3). Moreover, the future developments of each antibody are reported, based on current knowledge.

Table 1. Monoclonal antibodies development pathway in (phase II and phase III Randomized controlled trials)

Sl No.	Name	Description	Half-life (T1/2)	Phases	Study population	Dose	Adverse events
1	ALD403/ eptinezumab	Fully humanized IgG1, targets CGRP	31 days	Phase IIa in EM	163 (18-55) years old	1000mg IV single dose.	Upper respiratory tract infection, urinary tract infection, fatigue, backpain, arthralgia and nausea
				Phase IIb in CM	617 (18-55) Years old	30mg,100mg,300mg IV single dose	Respiratory infection, dizziness nausea, pharyngitis, sinusitis, and bronchitis
				Phase III PROMISE 1 in EM	900	300mg, 100mg, 30mg IV single dose	Upper respiratory infection, nasopharyngitis and sinusitis
				PROMISE 2 in CM	1121	100mg, 300mg single IV dose	upper respiratory tract infection, urinary tract infection, dizziness, arthralgia, fatigue, anxiety.
2	AMG-334/ erenumab	Fully human IgG2λ, targets CGRP receptor	21 days	Phase II in EM (continued open -label extension)	483	70mg SC every 4 week for 12 weeks	Nasopharyngitis, headache, nausea and upper respiratory tract infection
				Phase II in CM	667	70mg,140mg SC every 4 week for 12 weeks	injection site pain, upper respiratory tract infection and nausea.

				Ongoing Phase III in EM (STRIVE)	955	70mg,140mg SC every 4 week for 6 months	Nasopharyngitis, URTI, sinusitis, constipation, arthralgia, fatigue, nausea, influenza, UTI, back pain, injection site pain, hypertension.
				Ongoing Phase III (ARISE)	577	70mg SC every 4 week for 12 weeks	URTI, injection site pain, nasopharyngitis, influenza, fatigue, nausea, sinusitis
				Ongoing Phase IIIb in refractory EM (LIBERTY)	246	140mg SC every 4 week for 12 weeks	N/A
3	TEV-48215/ fremanezumab	Humanized IgG2k, targets CGRP	40-48 days	Phase II in high frequency EM	297	225mg or 675mg SC every 4 week for 12 weeks	Injection site pain, bronchitis, sinusitis, URTI, dizziness, fatigue, nasopharyngitis, back pain.
				Phase II In CM	264	675mg, 675 mg/225mg ,900mg once SC 4week for 12 weeks	Headache, sinusitis, paresthesia, UTI, back pain, injection site pain
				Phase III in EM(HALO)	875	225mg, SC for 3months 675mg at initiation followed by placebo for 2 months	Back pain, nasopharyngitis, injection site pain, sinusitis
				Phase III in CM (HALO)	1130	675mg, SC at initiation followed by 225mg for 2 months	URTI, nausea, dizziness, injection site pain.
4	LY2951742/ galcanezumab	Humanized IgG4, targets CGRP	28 days	Phase II in EM	218	150mg, SC every 2 weeks	Upper respiratory tract infection, Injection site pain, Back pain, Abdominal pain, Arthralgia, Injection site erythema, Dizziness, Rash, Hypertension, Neck pain, Pain in extremity, Nausea, Toothache, Sinusitis, Viral gastroenteritis
				Phase III in EM (EVOLVE-1 and EVOLVE-2)	862	120mg, 240mg SC monthly	Injection site, Upper respiratory tract infection, Nasopharyngitis, Urinary tract infection, Injection site erythema, Injection site pruritus, Injection site, Sinusitis, Nausea, Back pain, Dizziness, Bronchitis, Cough, Fatigue, Influenza
				Phase III in CM (REGAIN)	1113	120mg, 240mg SC monthly	Injection site pain, Nasopharyngitis, Injection site reaction, Upper respiratory tract infection, Injection site erythema, Nausea, Dizziness, Fatigue, Sinusitis

EM = episodic migraine; CM = chronic migraine; SC = subcutaneously; IV = intravenously; CGRP = calcitonin gene related peptide; Ig = immunoglobin.

CONCLUSION

Migraine is one of the most prevalent health problems globally characterized by considerable disability in every aspect of life. Activation of trigeminal nerves triggers release of CGRP and other peptides. CGRP is believed to play integral role in migraine pathophysiology by facilitating cellular events. Phase II and Phase III of Clinical trials conducted till date developed four monoclonal antibodies for migraine prophylaxis showed modest efficacy and safety potency which due to its high molecular weight is administered parentally. mAB have shown to reduce numbers of headache days. They appear to propose promising strategies for migraine prevention so far.

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Cite this article as:

Pem Tamang. Role of calcitonin gene related peptide in development of mAB in migraine: A review. Int. Res. J. Pharm. 2018;9(12):18-22 http://dx.doi.org/10.7897/2230-8407.0912285

Source of support: Nil, Conflict of interest: None Declared