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Review Article

Rimegepant in the Treatment of Migraine

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Abstract

Migraine is a common and chronic disorder with significant financial and socioeconomic burden. It is the 2nd most common reason for the years lived with disability after back pain. Current available treatment of migraine is limited to subpopulation due to poor tolerability, efficacy, side effects, contraindication and drug-drug interactions. So there is need to evolve some treatment to overcome these limitations. Calcitonin-gene-related peptide receptor has been identified in the pathophysiology of migraine over 30 years and in recent few years, some CGRP-receptor antagonists have been identified and can reduce the unmet needs in the treatment of migraine. This article is focused on exploring the role of rimegepant (CGRP-receptor antagonist) by reviewing myriads of articles published in Pubmed and Google scholar.

Keywords: Rimegepant; CGRP; Triptans; Migraine; Receptor antagonist

1. Introduction

The word migraine is derived from Greek word "hemikrania" which means "half of the skull" as in many cases of migraines patient presents with unilateral

headache which is throbbing or pulsating in nature .Migraine is a complex, recurrent headache disorder which is common complaint in hospitals.In USA more than 30 million people experience 1 or more episodes of headache per year. It is three times more common in females than males [1]. Currently one in every 6th American female has migraine. According to a study done in Philadelphia County in 1998, one year prevalence of migraine was 17.2 % in females and 6% in males [1]. Migraine has strong genetic inheritance with risk of migraine four times increased in relatives of the patient having migraine with aura [2]. Non syndromic migraine is multifactorial whereas rare migraine associated with certain syndromes has autosomal dominant pattern [3]. Familial hemiplegic migraine (FHM), MELAS (mitochondrial encephalopathy, lactic acidosis, strokes) and CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) are some disorders which also have migraines. Some of the identified precipitants of migraines are hormonal changes(menstruation [4], 50% females relate migraine to menstruation, pregnancy), stress, sleep changes, weather change, motion sickness, head trauma, lack of exercise, smoking, exposure to sunlight, strong odors (perfumes, colognes), drugs (vasodilators, oral contraceptives), fasting, cold stimulus (ice cream) and certain foods (caffeine, citrus fruits, aged cheese, red wine, meats containing nitrites.

Patient is usually awake when they develop pulsatile or throbbing pain mostly in frontotemporal region, which builds up in 1-2 hours, typically lasts 4-72 hours. Pain is associated with nausea and vomiting, photophobia or phonophobia, lightheadedness, vertigo, confusion, food cravings, mood changes and diarrhea or constipation. Migraine aura is complex neurological symptoms that may precede or accompany headache phase of migraines, develops over 5-20 mins and lasts less than 60 mins. Auras may be visual, sensory motor or in any combination. Negative visual auras include homonymous hemianopsia, tunnel vision, central scotomas or complete blindness. Positive visual auras are scintillating scotoma most commonly. Paresthesias and numbness are most sensory auras and usually follow the visual auras. Motor auras are usually heaviness of an extremity without weakness, speech and language disturbance and usually follow sensory auras.

1.1 Treatment of migraine aims at abortive therapy and prophylactic treatment

1.1.1 Abortive therapy:

Moderate pain: NSAIDS are used for the acute treatment of moderate pain

Severe pain: Tripatans are used for severe treatment

Extremely severe pain: Intravenous dihydroxyergotamine or opoids are used for extremely severe pain.

1.1.2 Prophylactic therepy: This arm of treatment aims at reducing frequency and severity of attacks. Methysergide (5-HT2 receptor antagonist), calcium channel blockers, beta blockers and tricyclic antidepressants are used as prophylactic therapy.

2. Mechanism of Action of Rimegepant

2.1 CGRP and migraine

Calcitonin gene-related peptide (CGRP) plays a vital role in migraine pathology as is evident from:

1 During migraine attack, CGRP levels are increased [5, 6].

2 Migraine attacks can be induced by intravenous infusion of CGRP [7, 8].

3 During a migraine attack, administration of sumatriptans causes decrease in CGRP level resulting in headache resolution [9].
4 Increased levels of CGRP are seen in chronic migraineurs [10].
5 Increased levels of CGRP are seen in jugular veins of humans and cats when trigeminovascular system is stimulated [11].

2.2 Rimegepant

Rimegepant is a competitive and selective receptor antagonist of human Calcitonin gene-related peptide (CGRP) [12] and was shown to be more efficacious in the treatment of acute migraine than placebo [13]. In a clinical trial, 19.6% of the patients being treated with rimegepant showed pain improvement at 2 hours of treatment as compared to 12% in placebo group ($p<0.001$) [14]. Sustained pain freedom, 2-24 hours was 42.6% for rimegepant and 26.55 for placebo ($p<o.ooo1$). Similarly Sustained pain freedom, 2-24 hours was 52.9% for rimegepant and 36.1% for placebo ($p<0.0001$) [15].

3. Discussion

Migraine is the one of the most common neurological problem nowadays and it affects the 14% of the whole world population [14]. The drug most commonly used i.e. triptans, ergots, non-steroidal, anti-inflammatory drugs, opioids and acetaminophen for migraine has a lot of side effects and contraindications. Triptans being the most commonly use as abortive drug has only 34 % good response while around 40% of these patients have recurrence of pain [16] with severe cardiovascular side effects. Thus, there is need to find out an effective abortive drug for migraine. A lot of Randomized control has been done to find out the efficacy of novel drug Rimegepant.Croop R *et al.* conducted a randomized clinical trial in which they assigned 732 patients to Rimegepant and 734 to placebo (total 1466 patients). Out of 1466 only 1351 patients were evaluated for efficacy (rimegepant n=669, placebo n=682). After 2 hour post dose administration, rimegepant was found superior in efficacy [freedom from pain] than placebo (21% vs 11%, $p<0.0001$ with 95% CI of 6-14) and was superior in freedom of bothersome symptoms (35% vs 27%, $p=0.0009$ with 95% CI of 3-13) [13]. In another randomized controlled trial conducted by Marcus R *et al.* in which they assigned three groups to either different doses rimegepant (BMS-927711) sumatriptan 100mg and placebo. Rimegepant and sumatriptan were found superior in efficacy regarding pain improvement than placebo after one hour of administration. Patients on rimegepant 75mg (31.4%, $p=0.002$), 150mg (32.9%, $p<0.001$) and 300mg (29.7%, $p=0.002$) had pain freedom and sumatriptan group (35%, $p<0.001$) had pain freedom as compared to placebo (15.3%) [17].

Bixi Gao *et al.*conducted a study on the efficacy and safety of rimegepant in migraine patients. They collected data of 3827 patients from four randomized controlled trial and studied freedom from pain, pain relief and relief of disturbing symptoms in these patients post 2 hour of administration of 75mg of rimegepant or placebo. They concluded that 75mg rimegepant has highly efficacy in freedom from pain ($p<0.001$), pain relief ($p<0.001$) and freedom from disturbing symptoms ($p<0.001$) and no increase in side effects [18]. Rimegepant and other gepants has safer cardiovascular profile as compare to triptans. Previously Triptans were the main treatment options for migraine but literature showed that 10% of those patients who were receiving triptans developed cardiovascular system and thus they are contraindicated in the cardiac patients [18]. A meta-analysis conducted by Kristian Thorlund *et al.*

concluded that triptans are associated with increase in chest discomfort as compared to placebo [19]. On the other hand, calcitonin gene related peptide antagonists have no cardiovascular adverse effects because they did not cause vasoconstriction of coronary vessels and could decrease cardiovascular events [20, 21]. Because of its efficacy and safe cardiovascular profile, FDA has recently approved Rimegepant as an abortive treatment option for acute migraine with or without aura [22].

4. Conclusion

Rimegepant has clearly shown to be as effective as triptans in the treatment of acute migraine with lesser cardiovascular side effects as compared to triptans. There are no absolute contraindications to its use and FDA recently approved it for the treatment of migraine as an abortive therapy. As compared to other Gepants, Rimegepant has no hepatotoxic effects. Thus it is recommended to use this drug as a first line drug for the treatment of acute migraine especially in patients in whom triptans are contraindicated.

Conflict of Interest

The authors declare no conflict of interest.

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