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General

Eptinezumab-jjmr, a humanized monoclonal specific to Calcitonin Gene Related Peptide, for the preventive treatment of migraine in adults

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Purpose of Review

Migraines are prevalent and cause significant morbidity, decline in quality of life and healthcare costs universally. Treatment options are varied, but efficacy is limited. This review centers on Eptinezumab-jjmr, a humanized monoclonal specific to CGRP for the prevention of migraines in adults. Herein presented are the science and mechanism of action, indication and clinical evidence for use.

Recent Findings

Migraines are severe, recurrent headaches, which are either episodic or chronic in nature. The pain is severe, often accompanied by co-morbid symptoms, such as photophobia, phonophobia, nausea and emesis, and is limiting in nature. It is a prevalent disorder that causes significant, worldwide disability, morbidity, suffering, and costs.
The pathophysiology of migraines is actively studied, though recent research points to an initiating event causing migraine generation, that is then propagated by other brain regions, a significant one being the trigeminocervical complex. This is driven by biochemical transmitters, chiefly CGRP. This discovery led to the development of CGRP-targeting drugs, including gepants (small molecular antagonists) and anti-CGRP antibodies, such as Eptinezumab-jjmr.
Traditional therapy includes preventative and abortive treatment; however, adherence with preventative treatment has been historically poor, and certain types of abortive therapy carry risks and side effects that preclude them from a large patient population. Moreover, traditional therapy often falls short in migraine therapy. CGRP antagonist, including Eptinezumab, aims to cover the gaps in migraine therapy. We present here evidence to support the safe and effective use of Eptinezumab for the prevention of migraines.

Summary

Migraines are a prevalent primary headache disorder causing significant morbidity worldwide. Traditional abortive and preventative treatments fall short for many patients. Eptinezumab is part of new generation of CGRP-targeting medications and has shown

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significant evidence to support its use for the prevention of migraines. Further research is required to properly compare eptinezumab with existing pharmacotherapy and update guidelines on the appropriate combinations of therapies that are not available and the correct patient selection for each.

INTRODUCTION

Migraines are severe, recurrent headaches, usually unilateral and pulsatile in nature. They are sometimes accompanied by a sensory aura that precedes the headache and could be perceived as visual, auditory, or olfactory changes. To be classified as a migraine, the headache must recur at least five times if it is not accompanied by an aura or occur at least twice with an aura. The pain is described as moderate to severe, and usually results in avoiding routine physical activities, such as climbing a flight of stairs) or is significantly exacerbated by these activities. Patients will often experience associated photo- and/or phonophobia in addition to nausea.[1,2] The burden of migraines on society has been well documented, with approximately 12% of Americans affected. Migraines are the fifth most common reason for an emergency department visit. Women are more frequently affected than males (17.1% versus 5.6% prevalence, respectively), and there is a disproportionate affect in low socioeconomic layer of society.[3–5]

Migraines are classified as either with or without aura, and as episodic or chronic. In patients who experience migraines with aura, the onset of headache is associated with either visual, sensory or, less commonly, speech disturbances. Visual disturbances are most common, often manifesting as a kaleidoscope of shimmering or flashing lights in the peripheral vision.[1–3] Migraines can be further classified as either episodic or chronic based on the frequency that migraines occur over the course of a month. Typically, chronic migraines will manifest due to progression of episodic migraines secondary to underlying risk factors, accounting for 8% of patients with migraines, which equates to approximately 1-2% of the general population. Despite the small representation in the general population, chronic migraines are significantly debilitating; significantly impact quality of life and socioeconomic standing in a negative way; and are often attributed to modifiable risk factors such as overuse of migraine medications, obesity, depression and stressful events.[1,3,6] Current therapies for acute migraines include triptans, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, acetaminophen, ergots, opioids and anti-emetics.[7] Novel research led to the identification of calcitonin gene-related peptide (CGRP), an endogenous peptide that likely has a significant role in the initiation and propagation of migraines. Several medications targeting CGRP, such as Galcanezumab and Fremanezumab, have already been made available and are making a significant difference in the migraine treatment landscape.[8–10] Another promising new treatment is eptinezumab, a monoclonal antibody directed against calcitonin gene-related peptide (CGRP), a key factor in the pathophysiology of migraines, that shows promise in preventing chronic migraines.[11,12]

MIGRAINES

Headaches are one of the most experienced symptoms worldwide, occurring in 96% of individuals at least once at some point in their lives with females being predominantly affected. Headaches are classified as primary, secondary, or other headaches. Primary headaches, which are characterized as dysfunction or over-activity of nociception and processing, consist of migraines, tension-type headaches, and trigeminal autonomic neuralgia, thus accounting for most headache disorders. Secondary headaches are headaches that occur secondary to an underlying illness and cover a larger distribution of etiologies, including psychiatric, infectious, substance use, and head trauma, among others. The two most common primary headache disorders are tension headaches and migraines.[13,14]

EPIDEMIOLOGY

Affecting nearly one in seven Americans with a 14.9% three-month prevalence, multiple population-based studies have shown a relatively stable prevalence.[15] Recent studies, however, have offered alternatives to the actual prevalence in the American population given that many of the population studies are conducted using surveys rather than requiring evidence of a definitive diagnosis. In one such study, a comparison of migraine prevalence in neurologists versus non-neurologists showed a statistically significant difference, with neurologists displaying a prevalence two to three times greater than previously reported population prevalence values.[16] The global burden of migraines was found to be even greater at 14.4% compared to 12% in the American population.[3] Regardless, there is exhaustive evidence that certain populations are disproportionately affected. Females are affected at a ratio of, at minimum, 2:1 compared to males. More recent studies have shown 18% of females and only 6% of males are affected by migraines in the United States. Furthermore, individuals who are unemployed or only part-time employed display a greater prevalence. This result extends to income as well, with an inverse relationship between income and migraine prevalence being noted in several population studies.[4,15,17,18]

PATHOPHYSIOLOGY

While the underlying pathophysiology of migraines has yet to be fully elucidated, significant advancements have been made. Specifically, current literature indicates that migraines consist of a synchronous excitability involving a complex brain network composed of multiple discrete brain regions, including the trigeminal vascular system, brainstem nuclei, hypothalamus, thalamus and cortex.[19] Structural studies regarding differences in brain structure in healthy controls and patients with migraines have identi-

fied numerous regions that consistently display discrepancies between the two groups.[20] Additionally, evidence of genetic predisposition has emerged with the discovery of genes responsible for familial hemiplegic migraine and the understanding that migraines tend to occur in patients with a known family history. While multiple loci have been identified in association with migraines, the most likely role of genetics in migraine prevalence consists of interaction between multiple genomic foci in addition to epigenetics.[21,22]

Current theories regarding the origination of migraines in the brain network point to brainstem regions serving as the 'migraine generator' remain in debate, but evidence has emerged that identified particular regions responsible for influencing pain processing modulation in the trigeminocervical complex (TCC).[23] Transmitters released in the brainstem that target the TCC have been implicated in the role of migraine onset and serve as a target for migraine therapies, including the calcitonin gene-related peptide (CGRP) targeted by eptinezumab. Specifically, CGRP has been suggested to serve a modulatory role in the pathophysiology of migraines and nociceptive transmission in the trigeminovascular system.[19,24,25] The hypothalamus has been implicated in the role of producing the prodromal symptoms of yawning, irritability, and food cravings. The thalamus serves as a central area through which input and subsequent transmission to various brain regions occurs. When this thalamocortical transmission is disrupted, sensory hypersensitivity and allodynia occur, producing the classic symptoms of photophobia and phonophobia. Evidence from multiple studies have identified structural and functional changes involved in the cortical wave of depolarization resulting in the manifestation of the migraine aura and cognitive symptoms.[19,21,26]

RISK FACTORS FOR MIGRAINES

Despite the relative ambiguity surrounding the pathophysiology of migraines, evidence has shown that migraines rarely occur spontaneously. Indeed, systematic literature review has identified several risk factors or triggers that often precede migraines, the most common of which is stress. The exact timing of stress and migraine onset, however, remain unknown as various studies have shown increased stress can precede migraines by several days while others indicate that elevated stress only occurred in the day preceding migraine onset. Other triggers of migraines include auditory stimuli, fatigue, fasting, sleep deprivation, visual stimuli, olfactory stimuli, alcohol and weather changes.[27] While these triggers have been cited in various studies, the most well studied and accepted trigger of migraines is the menstrual cycle. Specifically, low estrogen levels are associated with increased risk for developing migraines and, notably, these menstrual migraines tend to be more severe and resistant to treatment.[27,28] Furthermore, risk factors for migraine progression from episodic to chronic have also been identified. These risk factors can be divided into two categories: modifiable and non-modifiable. The modifiable risk factors include obesity, medication overuse, excess caffeine intake, increased stress, psychiatric conditions such as anxiety and depression and sleep disorders. Non-modifiable consist of gender, age, race and socioeconomic status.[29–31]

DIAGNOSIS AND CLINICAL PRESENTATION

The clinical manifestations of migraine are diverse and myriad, which makes the development of diagnostic criteria exceedingly difficult. Generally, migraines are characterized as unilateral, throbbing headaches that are often accompanied by photophobia, phonophobia, allodynia, nausea, and emesis. Additional neurological manifestations of symptoms can also occur, ranging from vertigo to cognitive impairment.[2,22] Migraines are often heralded by premonitory symptoms that occur in the hours to days before migraine onset. Patients typically note increased irritability, yawning, particular food cravings and muscle fatigue. In patients who experience migraines with aura, they can develop visual disturbances, temporary vision loss and paresthesia in the minutes preceding migraine onset.[32]

Current International Classification of Headache Disorders (ICHD-3) diagnostic criteria for migraines are divided into migraines with and without aura. However, what these diagnostic criteria fail to capture is the nuanced presentations of migraines that do not fit diagnostic criteria but would still be treated as a migraine by neurologists. Therefore, it is important to view the ICHD-3 diagnostic criteria more as a guideline for assessing patients with suspected migraines versus a definitive and exhaustive list of migraine-classifying signs and symptoms.[32–34]

CURRENT TREATMENT OPTIONS

ABORTIVE AND PREVENTIVE TREATMENT

Current migraine treatments are broadly categorized as either abortive treatments or preventative (prophylactic) therapy which are utilized with consideration of evidence-based guidelines and individual patient needs.[35–37] Abortive treatments are used for symptomatic relief in the setting of acute migraine attacks.[35,38] A well-established principle for improved abortive treatment outcomes is the rapid initiation of therapeutic intervention after the onset of migraine symptoms.[21,22,35,38] Standard abortive pharmaceuticals can be distinguished as non-specific such as non-steroidal anti-inflammatory drugs or migraine-specific drugs including triptans and ergot derivatives.[7,39,40] In contrast to abortive treatment, preventive therapies are taken on a routine basis with the goal of reducing headache frequency, severity and duration in an effort to minimize disability and improve quality of life in patients who experience frequent migraine attack.[35,38,41] While the leading evidence-based preventive pharmaceuticals mainly consist of onobotulinum-A (OBT-A) injections and topiramate, it is important to note that a variety of existing oral medications have been repurposed rather than specifically designed for migraine treatment.[22,35,41] Abortive treatment is necessary in all migraine patients while preventative treatments are typically recommended for all chronic migraine (CM) patients and approximately one third of episodic migraine (EM) patients.[19,37]

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Over-the-counter (OTC) non-opioid analgesics and NSAIDs are the most commonly used abortive medications and are utilized as first-line agents for mild to moderate migraines.[39] Acetaminophen (paracetamol), which is thought to provide analgesic effects via cyclooxygenase (COX) inhibition in the central nervous system, has demonstrated efficacy as an abortive migraine treatment with a relatively mild side effect profile.[35,42] NSAIDs with known efficacy in migraine management include aspirin, diclofenac, ibuprofen, and naproxen, which act by non-selective inhibition of COX-1 and COX-2.[40] NSAIDs offer the benefits low cost and ease of accessibility[42]; however, the risk of GI bleeding and adverse cardiovascular effects with NSAID's limits the safety of use in patients with known risk of bleeding or existing cardiovascular disease.[35,40]

5HT AGONISTS

Triptans were developed almost 30 years ago and are still considered the gold standard first-line therapy for moderate to severe migraine attacks.[7,43,44] Triptans act as selective agonists of the serotonin $5HT_{1B/1D}$ receptor resulting in vasoconstriction via $5HT_{1B}$ receptors on cranial blood vessels and inhibit nociceptive neurotransmission in peripheral and central trigeminal neurons via $5HT_{1B/D}$ receptors.[39,45] 7 different triptans are currently available as tablets, with the added versatility of additional formulations such as sumatriptan and zolmitriptan as a nasal spray nasal and orally disintegrating rizatriptan and zolmitriptan.[7,46–48] Historically, triptans have been contraindicated in patients with existing cardiovascular disease due to potential risks associated with vasoconstrictive effects on coronary arteries.[44,45,49] Low rates of treatment persistence and poor tolerability also limit the efficacy of triptans.[40]

A promising alternative to triptans are ditans, such as lasmiditan, a novel selective $5\text{-}HT_{1F}$ receptor agonist in clinical trials that provides acute migraine relief without the vasoconstrictive effects of $5\text{-}HT_{1B}$ agonism. Preclinical models propose that Lamiditan modifies neurogenic inflammation and nociceptive activation of the trigeminovascular system.[44,50] In addition to enhanced cardiovascular safety, Lasmiditan has demonstrated favorable efficacy with minimal side effects.[46,50]

TIMING, LIMITATIONS, CONTRAINDICATIONS FOR ACUTE THERAPY

Despite the necessity of acute therapies for all migraine patients, treatment needs are often unfulfilled due to side effects and limitations in the efficacy of abortive drugs.[40] A substantial portion of migraine patients have comorbidities that preclude them from using acute medications.[38] Inadequate abortive treatment also poses the risk of disease progression from EM to CM.[35,38,51] Furthermore, frequent use of symptomatic medication may increase the risk of transformation of EM to CM and can lead to medication overuse headaches. Migraine over-use headaches are defined as occurring ⩾ 15 days per month as a result of routine use of abortive medications in excess of recommended monthly frequencies.[22,40] The limitations of acute therapy highlight the need for effective preventive treatments.

TOPIRAMATE

A variety of randomized control trials have demonstrated the utility and safety of Topiramate, an antiepileptic drug, in EM prophylaxis and CM treatment.[52] Topiramate acts via blockade of calcium and voltage-gated sodium channels in addition to inhibiting excitatory glutamate and GABA effects.[52] The therapeutic effect of Topiramate in migraine involves suppression of cortical spreading depolarization and inhibition of neuronal hyperexcitability.[41,53] Compared to OBT-A, Topiramate is associated with more common side effects including altered memory and concentration, fatigue, nausea and paresthesia.[41,52] Topiramate is also teratogenic and therefore contraindicated in women who may potentially become pregnant without a reliable method of contraception.[35]

ADHERENCE ISSUES WITH CHRONIC PREVENTATIVE THERAPY

Despite continued advances, migraine management continues to be less than optimal.[40,43] Compliance with preventive treatment regimens is notoriously low with only 3-13% of migraine patients utilizing preventive treatment.[35] The lack of migraine-specific preventive medication options, sub-optimal efficacy, and poor tolerability are significant factors that have contributed to poor compliance.[37]

CGRP MODULATION

The growing consensus regarding the involvement of CGRP in neurovascular pain transmission during migraine pathogenesis has paved the way for the development of novel CGRP modulating agents which selectively intercept nociceptive signaling by targeting CGRP neuropeptides and respective CGRP receptors.[19,21,54]

Gepants are small molecule CGRP receptor antagonists that were recently developed for use in acute migraine therapy.[55] Notably, gepants have demonstrated comparable efficacy to triptans without the vasoconstrictive side effects associated with triptans.[55] Phase 3 clinical trials have been completed for Ubrogepant and Rimegepant, with recent FDA approval of Ubrogepant as an acute migraine treatment.[40,56] Further studies continue to investigate Atogepant and Rimegepant as potential prophylactic treatments for EM.[41,55,57]

Four CGRP Monoclonal Antibodies (mAbs) were recently introduced and FDA approved as an additional class of novel drugs for the prevention of EM and CM with evidence of considerable safety, efficacy, and tolerability.[58,59] As the first prophylactic drugs designed specifically for migraines, CGRP mAbs offer the benefits of a long half-life with intravenous or subcutaneous dosing at 4-12 week intervals and precise targeting of CGRP (Erenumab) or the CGRP receptor

(Eptinezumab, Fremanezumab, Galcanezumab) that minimizes the risk of drug interactions and toxicity.[8,9,51,57,60] CGRP mAbs such as eptinezumab serve as a promising new treatment option for patients who have failed to achieve relief with prior treatments or suffer from medication overuse headaches.[58]

INJECTION AND INTERVENTIONAL THERAPY

Onobotulinum-A (OBT-A) was shown to be effective for chronic migraine prevention, with a relatively mild side effect profile, in the PREEMPT trials that resulted in FDA approval in 2010. OBT-A is thought to counteract activation of trigeminal nociceptive neurons by modulating the release of neurotransmitters such as CGRP, glutamate, substance P, and GABA and affecting pain receptors.[8,41,46] OBT-A is recommended as a second-line treatment when common oral medications fail or prove to be intolerable. The recommended administration of OBT-A every 3 months via injections in 7 head and neck muscles, make this a convenient long-term treatment option.[41]

Acupuncture, dry needling, and regional nerve blocks have also been described and found effective for abortion of migraines, however, they require in-person administration by trained professionals and an increasing level of invasiveness.[61–63]

EPTINEZUMAB-JJMR

Eptinezumab-jjmr, also known as Vyepti, ALD403, or eptinezumab, is a humanized monoclonal antibody that selectively binds to calcitonin gene-related peptide (CGRP) thereby preventing CGRP from binding to its receptor.[64] This drug was developed by Lundbeck Seattle BioPharmaceuticals as an intravenous (IV) treatment for the prevention of migraines.[64] The drug is packaged as a 100 mg/mL single dose vial that must be diluted in 0.9% normal saline for intravenous delivery over a period of 30 minutes. Eptinezumab is stored refrigerated at 2° C to 8° C in the original carton to protect against light until time of use.[65]

APPROVAL AND GUIDELINES

Eptinezumab was approved by the Food and Drug Administration (FDA) on February 21, 2020 for the preventative treatment of migraine in adults. The drug is given via a 30-minute IV infusion every three months with a standard dose of 100 mg, although a 300 mg dose may also be considered for patients.[66] As of December 23rd, 2020, eptinezumab is not approved for the treatment of migraines in adults by the European Medicines Agency (EMA) but has been accepted for a marketing authorization application. This authorization is the beginning of the formal review process required before eptinezumab can be approved by the EMA.[67] The European Headache Foundation issued a guideline in 2019 recommending monoclonal antibodies acting on CGRP for migraine prevention.[68]

DEVELOPMENT

Eptinezumab is a genetically engineered humanized monoclonal antibody, or mAb (IgG1), that is derived from yeast (*Pichia pastoris*).[69] The Complementarity Determining Region (CDR), which are grafted to human Fab regions, are derived from rabbit, thus resulting in the anti-CGRP-mAb-grafted CDR known as eptinezumab.[70] Its target, CGRP, has been shown to be the only neuropeptide released during the headache phase of migraine attacks. CGRP modulates the function of other neurotransmitters and affects pain transmission and inflammation. It is especially prominent in the trigeminal nerve endings, where elevated CGRP release has been associated with neurogenic inflammation.[71] Additionally, a 2018 study found that elevated CGRP provokes cluster headache attacks.[72] The antibodies enter the vascular endothelium via pinocytosis before binding to its target.[73] Eptinezumab binds to both the α and β isoforms of CGRP, preventing its accumulation and activation, that in excess, leads to painful headache episodes.[74] It is a large sized protein, and therefore cannot cross the blood brain barrier (BBB), thus binding to CGRP occurs in areas such as the trigeminal afferent nerves.[75] Its humanized Fc domain is highly specific and minimizes interactions with complement or other immune-functions.[76] Three other mAb drugs effecting CGRP have been studied. Two drugs have similar activity against CGRP, including fremanezumab and galcanezumab, while the drug erenumab targets the CGRP receptor directly.[73]

PHARMACOKINETICS AND DOSING

Eptinezumab has a volume of distribution of 3.7 L with a biological half-life of 27 days. It demonstrates linear pharmacokinetics, with steady-state plasma concentrations reached after the initial dose (100 mg to 300 mg), given intravenously once every 3 months.[76,77] It has a maximal serum concentration (Tmax) of 4.8 hours after intravenous delivery. In comparison with similar mAb therapies being investigated, such as fremanezumab and galcanezumab, eptinezumab associates rapidly and dissociates more slowly from its therapeutic target.[73] There is no proof that eptinezumab crosses the placental barrier.[70]

ADVERSE EFFECTS

A 2019 meta-analysis found no difference in adverse effects between eptinezumab and placebo, but cited only one study.[59] A 2020 phase 3 multicenter, randomized, double blind study known as Prevention of Migraine via Intravenous ALD403 Safety and Efficacy-2 (PROMISE-2) found no significant difference between adverse effects of eptinezumab and placebo, including nasopharyngitis, upper respiratory tract infection, sinusitis, migraine, urinary tract infection, nausea, and fatigue.[78] A Japanese clinical trial examining the safety and pharmacokinetics of eptinezumab is currently being performed.[79] Eptinezumab was not found to precipitate an immune system response.[76] However, seven patients withdrew from the Prevention of Migraine via Intravenous ALD403 Safety and Efficiacy-1

(PROMISE-1) randomized clinical trial due to hypersensitivity reactions (1.1%, n=7).

EPTINEZUMAB-JJMR FOR MIGRAIN PREVENTION – CLINICAL DATA

EFFICACY & SAFETY PROFILE

In phase I trials of eptinezumab, 100 participants received ascending dosages either intravenously or subcutaneously. For the 1000mg IV group, a half-life of approximately 32 days was determined with linear pharmacokinetics for dosages between 1mg to 1000mg. Additionally, no significant drug-drug interactions were seen with sumatriptan.[69]

Eptinezumab's phase II clinical trial included 174 participants aged 18-55 with more than 12 months of migraines including a diagnosis prior to 50 years of age. Participants had to experience between 5 and 14 migraines in the 28-days prior to the start of the study for inclusion. Patients with a history of certain types of headaches, including chronic tension, hypnic and sporadic headaches, were excluded as were patients with regular use of headache preventative drug with proven efficacy in a placebo-controlled trial within the 3 months prior to start of the study period. Efficacy was measured as a change from baseline to migraine frequency between weeks 5 to 8. Participants were divided into a 1000mg and placebo groups. Participants who received the 1000mg dose reported 5.6 fewer migraine days, a significant improvement from baseline, compared to 4.6 fewer migraine days reported by the placebo group. There were no differences in adverse effects between the 1000mg and placebo groups, nor were there any differences in laboratory safety data or vital signs.[80] In a comparative meta-analysis of eptinezumab and 3 other calcitonin gene-related peptide (CGRP) mAB, eptinezumab was the only drug not associated with increased adverse events or increased treatment-related adverse events.[59]

In its phase IIb clinical trial, 616 patients between the ages of 18 – 55 years with a diagnosis of chronic migraine (CM) (diagnosed at least 1 year prior and onset before age 35) were administered a single IV dose of either eptinezumab 10mg, 30mg, 100mg, 300mg, or placebo on day 0. Prior to the study period, participants had to have had at least 15 headache days in the 28-day screening period, including over 8 migraine days and over 5 migraine attacks. Primary efficacy was measured by percentage of patients with over 75% decrease in monthly migraine days over weeks 1 – 12 compared to the 16 mean migraine days for all treatment groups in the 28-day runup to the trial period. Mean monthly migraine days decreased across all treatment groups (baseline 16.5 to 8.3 for 300mg; baseline 16.9 to 9.3 for 100 mg; baseline 16.2 to 8.3 for 30 mg; baseline 16.4 to 9.7 for 10 mg; baseline 16.4 to 10.9 for placebo). Over weeks 1 – 12, 33.3% of 300mg participants, 31.3% of 100mg participants, 28.2% of 30mg participants, 26.8% of 10mg participants versus 20.7% of placebo participants reported a greater than 75% reduction in migraine days, with the greatest benefit seen with the 300mg group. Secondary efficacy measures, including decrease in percentage of severe headaches, favored eptinezumab administration in all dosages versus placebo. Treatment-emergent adverse events were evenly distributed amongst all study groups with no serious TEAEs attributed to the study drug.[81]

In PROMISE (Prevention Of Migraine via Intravenous eptinezumab Safety and Efficacy) 1, a phase III clinical trial, eptinezumab was administered in 30mg, 100mg, and 300mg doses in 888 patients with frequent episodic migraines compared to a placebo. Participants were given up to 4 IV doses every 12 weeks with efficacy measured as a reduction from baseline in mean monthly migraine days over weeks 1 – 12. All treatment groups saw a reduction in mean monthly migraine days compared to an average baseline of 8.6 migraine days in the 28-day run up to the study (baseline 8.7 days, -4.0 day reduction for 30mg; baseline 8.7 days, -3.9 day reduction for 100mg; baseline 8.6 days, -4.3 day reduction for 300mg; baseline 8.4 days, -3.2 day reduction for placebo).[82] One day after administration of eptinezumab, the probability of a migraine was significantly reduced from baseline for all treatment groups (45% reduction for 30mg; 51.3% reduction for 100mg; 53.6% reduction for 300mg) versus placebo (20.7% reduction).[83] Results in both primary and secondary efficacy measures for the 30mg group were found not to be statistically significant from those of the placebo group.[84] Subsequent exposure-response analysis has indicated 100mg as the lowest effective dose, with a similar efficacy between 100mg and 300mg doses due to a plateauing effect.[85] Adverse effects among the eptinezumab groups were similar to those experienced by the placebo group. Additionally, there were no serious adverse events attributed to the study drug.[82]

In PROMISE 2, a second phase III clinical trial, eptinezumab was administered to patients with a diagnosis of chronic migraine, compared to a diagnosis of episodic migraines in PROMISE I. Eptinezumab was administered to 1,072 participants at day 0 and again on week 12 in 100mg and 300mg groups compared to placebo.[86] Eptinezumab efficacy was measured over a 24-week period following drug administration. From a baseline of 57.5% days with migraine, 28.6% of participants in the 100mg group (50.3% reduction) and 27.8% of participants in the 300mg group (51.7% reduction) reported a migraine on day 1, 24 hours after administration of eptinezumab. These results are significantly different than those from the placebo group, in which 42.3% of participants (26.4% reduction) reported a migraine on day 1.[78] Additionally, eptinezumab recipients reported fewer mean monthly migraine days from a baseline of 16 monthly migraines during both the first dosing interval (weeks 0 – 12; - 7.7 days for 100mg, -8.2 days for 300mg, and -5.6 days for placebo) and the second dosing interval (weeks 13 - 24; -8.2 days for 100mg, -8.8 days for 300mg, and -6.2 days for placebo). Compared to the placebo group, the 100mg and 300mg eptinezumab groups demonstrated statistically significant improvements to migraine frequency across 24 treatment weeks (Silberstein et al., 2020). Improvement was also seen as measured by the Headache Intensity Test (HIT-6), a questionnaire commonly used to evaluate disability due to headache episodes in migraine patients.[87] Patients in the PROMISE-2 trial showed significant improvement in severe headache-re-

lated life impact. From a baseline of 89.6%, patients improved to 43.5% by week 24 in the 100mg group. From a baseline of 88.6%, patients improved to 39.7% in the 300mg group by week 24. From a baseline of 87.4%, patients improved to 55.3% in the placebo group by week 24. Overall, the percentage of patients who improved based upon patient reported outcomes were greater amongst the eptinezumab groups than the placebo group and improved after the second administration of eptinezumab in week 12.[86] There were no significant differences in TEAEs in the treatment groups versus the placebo group, of which the most frequent were fatigue in nausea. The only serious TEAE reported was worsening visual aura in a patient with a history of migraines with aura.[78] Additionally, the safety profile of the first dose was unchanged by the second dose at week 12.[86]

GUIDELINES

Candidates for eptinezumab include patients with frequent and/or severe migraines who do not respond to acute treatments. Patients at risk of developing headaches from medication overuse are also candidates for preventative treatment. There is no data on the effect of eptinezumab during pregnancy, nor is there data on eptinezumab presence in breast milk, milk production, or effects on breast fed infants. However, there were no pre- or postnatal developmental effects on rats given weekly large amounts of eptinezumab. The recommended dosage is 100mg over a 30 minute interval; however, some patient may require a 300mg dose for clinical benefit.[88] Dosage adjustments for patient characteristics (weight, sex, renal function) are not recommended.[85] Eptinezumab has no contraindications for patients with stroke, coronary artery disease, liver disease or kidney disease, and there are no significant interactions with other drugs known at this time.[89] Related to lack of renal clearance or hepatic involvement, eptinezumab may be used with concomitant drugs and with other antimigraine medications.[90] Monoclonal antibodies, including eptinezumab, are not suitable for oral administration due to their protein nature.[69] A summary efficacy, safety and comparative studies can be found in Tables 1 and 2.

CONCLUSION

Migraines are a prevalent, highly disruptive primary headache syndrome with significant consequences for many patients. Traditional abortive therapy, including NSAIDs, acetaminophen, and triptans has been used successfully for many years, but falls short in the case of frequent or severe migraines. And while acetaminophen is mostly well-tolerated, NSAIDs and triptans, especially when chronically used, carry significant risk for adverse events and are precluded in large part of the population. Traditional preventative treatment for migraines is only partially effective and seldomly well tolerated, explaining historically poor compliance.

Recent advances in research pointed to the TCC as a region of interest and identified CGRP as a key player in migraine propagation. Several CGRP antagonists have been developed recently, and these have generally belonged to either the small molecule antagonist family (gepants), or monoclonal antibodies, including Eptinezumab-jjmr.

Clinical trials provide evidence showing that Eptinezumab-jjmr is effective in both decreasing the number of migraine days, as well as the intensity of pain. It is also very well tolerated with minimal side effects. Head-to-head trials are few and it is hard to compare eptinezumab directly with either traditional treatment or new classes of medications, and further research will be required to define the role eptinezumab should play in multimodal treatment of migraines. With increasing use, hopefully information will be available to inform not only direct symptom resolution and prevention, but also improvement in quality of life, activity, and reduction of usage in medications.

ETHICAL CONSIDERATIONS

HCA Centralized Algorithms for Research Rules on IRB Exemptions (CARRIE)/ IRB manager issued study exemption # 2022-753.

CONFLICTS OF INTEREST

None of the authors report any conflicts of interest.

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DISCLAIMER

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Table 1. Summary of evidence comparing Eptinezumab-jjmr to existing and other therapies for migraines.

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Xu et al., 2019[59]	Meta-analysis of safety and tolerability of CGRP mAb, including galcanezumab, erenumab, fremanezumab and eptinezumab	No difference in occurrence of adverse events in eptinezumab 1000mg and placebo in phase II trial. Significantly higher rates of adverse events in galcanexumab 120mg with injection site erythema in 120mg and 240mg. Increased association of nasopharyngitis and pain at injection site with galcanezumab 150mg and 5mg. Higher rates of adverse events with 70mg and 140mg erenumab. Significantly increased treatment-related adverse events with fremanezumab 225mg/month and 675mg/quarter.	Unlink other CGRP mAb, eptinezumab was not associated with increased adverse events or treatment-related adverse events.
Ibekwe et al., 2018[91]	Analysis of phase II and III of 4 anti-CGRP monoclonal antibodies: eptinezumab, erenumab, fremanezumab, and galcanezumab	Each showed a statistically significant decrease in frequency of migraines for episodic and chronic migraine sufferers. No safety concerns were identified for any of the four drugs.	Anti-CGRP monoclonal antibody drugs show a strong safety and efficacy profile.
Mitsikostas et al., 2017[92]	Literature review of phase 2 CHRP mAbs: eptinezumab, erenumab, galcanezumab, and fremanezumab.	All four drugs show efficacy similar to that of current antimigraine drugs but have promising safety and tolerability profiles.	Larger scale studies are needed to study long term safety and tolerability profiles. Additional evaluation is needed for risk to pregnancy and cardiovascular effects.
Sacco et al., 2019[68]	Literature review on use of CGRP monoclonal mAbs.	Quality of evidence for eptinezumab, erenumab, fremanezumab and galcanezumab in treatment of episodic migraine is low to high. Quality of evidence for erenumab, fremanezumab, and galcanezumab for chronic migraine is medium to high.	Monoclonal CGRP mAbs drugs can be recommended for both chronic and episodic migraines. Additional data is needed to improve use of these drugs in clinical practice.

Table 2. A summary of clinical evidence supporting the efficacy and safety of Eptinezumab-jjmr.

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Silberstein et al, 2020[93]	1072 participants. Mean age of 40.5 years. 88.2% female. 91.0% white.	Significant reduction in migraine days over treatment period. Reduction to severe headache-related life impact.	Effective reduction in number and severity of migraines over treatment period
Dodick et al., 2014[80]	174 patients aged 18-55 with 5-14 migraines per 28-day period.	Significant reduction in mean migraine days over weeks 5-8 in 1000mg group compared to baseline.	Significant reduction in migraine frequency compared to baseline. No significant adverse effects found for 1000mg eptinezumab group compared to placebo.
Ashina et al., 2020[82]	888 participants aged 18-75 with a diagnosis of migraine	Reduction in mean monthly migraines across all treatment groups. Evenly disbursed TAEA across groups.	Unchanged safety profile. Minimum dosage of 100mg.
Dodick et al., 2019[94]	616 men and women with a diagnosis of chronic migraine (CM). 300mg, 100mg, 30mg, and 10mg groups versus placebo.	Significantly reduced mean monthly migraine days (MMMDs) compared to placebo across all eptinezumab groups, with greatest benefit seen in 300mg group.	Equal TEAEs across all groups. No serious TEAEs attributed to eptinezumab. Effective reduction of migraines favoring high dosage groups & well tolerated.
Saper et al., 2018[95]	See Ashina et. Al., 2020	Reduction in mean monthly migraine days, including reduction in migraines one day after administration.	Significant reduction in number of migraines from baseline and compared to placebo group.

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