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Eptinezumab: A calcitonin gene-related peptide monoclonal antibody infusion for migraine prevention

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Abstract

This article seeks to analyze the clinical trials concerning the newly approved eptinezumab to assess its efficacy, safety, and application to current clinical practice. The Institute of Health US National Library of Medicine Clinical Trials, PubMed, and Cochrane Library databases were searched for relevant abstracts, journal articles, and other published sources. Search terms included eptinezumab, Vyepti®, and ALD403. Relevant English-language articles were evaluated and included in the narrative. Two randomized controlled trials compared quarterly infusions of eptinezumab 100 mg, eptinezumab 300 mg, and placebo in chronic and episodic migraine sufferers. In episodic migraine, eptinezumab resulted in a reduction of approximately 4 monthly migraine days, which was significant compared to placebo. In chronic migraine, eptinezumab reduced monthly migraine days by approximately 8 days, also significant compared to placebo. More patients who received eptinezumab experienced at least 75% reduction in monthly migraine days compared to placebo, resulting in a number needed to treat as low as 6, depending on the study population and the dose. The preventive impact was noticed day one post-infusion. The most common treatment-emergent adverse events were nausea and fatigue, and there was a low incidence of hypersensitivity or study withdrawal. Eptinezumab is the fourth Calcitonin Gene-related Peptide monoclonal antibody to receive Federal Drug Administration approval. Its delivery as a quarterly infusion sets it apart from the other agents in this class. As an infusion, eptinezumab has a quick onset of action that may prove especially beneficial to those with severe or refractory episodic or chronic migraines, despite the perceived increased direct and indirect cost of an infusion.

Keywords

Eptinezumab, episodic, chronic, migraine, prevention, Calcitonin Gene-related Peptide monoclonal antibody

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Introduction

Migraine is pervasive and global, leading to disability, worsened quality of life measures, and reduced productivity.[1,2] It levys a costly economic burden on migraine sufferers, the medical system, and society at-large.[1,2] Migraines affect roughly 15% of the US population and are more likely to affect females between the ages of 18 and 44 years living below the federal poverty threshold.[3] Most migraine sufferers have episodic migraines, defined as <14 headache days and <8 migraine days per month.[4] Meanwhile, chronic migraine is defined as a headache on $\geqslant 15$ days per month, with $\geqslant 8$ migraine days.[4] Epidemiologic data have previously demonstrated that the majority of patients either do not receive appropriate preventive treatment or do not find sufficient relief.[5,6]

Until the approval of the first Calcitonin Gene-related Peptide (CGRP) monoclonal antibodies, migraine sufferers were relegated to non-specific agents for migraine prevention, such as beta-blockers, antiepileptics, and antidepressants. Many of these therapies carry adverse effect profiles that result in poor adherence.[7] As a class, CGRP monoclonal antibodies are Federal Drug Administration (FDA) approved to prevent migraine with minimal adverse effects. Eptinezumab is given quarterly as an intravenous (IV) infusion and has been studied in both episodic and chronic migraine with promising results. This review will discuss the efficacy, safety, and place

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in therapy of eptinezumab among migraine sufferers and within the CGRP monoclonal antibodies.

Pharmacology

As the pathophysiological framework that attempts to explain the migraine syndrome has changed, CGRP has demonstrated an increasingly important role in migraine. CGRP is a peptide neurotransmitter released from trigeminal ganglion cells, sensory neurons, and central nerve terminals.[8] It impacts pain transmission and is a potent vasodilator.[8] In addition, CGRP is involved in mast cell degranulation, ultimately resulting in a persistent pro-inflammatory sensitization of trigeminal nociceptors.[9]

As a class, the CGRP monoclonal antibodies prevent the action of CGRP by either binding to the CGRP ligand or the CGRP-receptor. Eptinezumab binds to alpha and beta forms of the CGRP ligand, preventing the ligand from binding to the receptor and blocking CGRP's downstream effects, like pain transmission.[10] Because the monoclonal antibodies are unable to cross the blood–brain barrier, the site of action is at peripheral CGRP sites such as trigeminal nerve projections outside of the blood–brain barrier or central nervous system sites without a blood–brain barrier.[10]

Eptinezumab is a 95% humanized IgG1 antibody.[11] The remaining 5% is murine, which accounts for the agent's low risk of hypersensitivity.[12] The quick onset and long half-life of eptinezumab is thought to be related to its quick association and slow dissociation with CGRP which has been demonstrated in vitro. Furthermore, at the equivalent circulating concentrations, eptinezumab binds to and inhibits CGRP twice as quickly as fremanezumab.[13] Based on pharmacokinetic and pharmacodynamic studies, eptinezumab demonstrates high affinity for both alpha and beta CGRP ligands (binding affinity constant 4×10^{-12} and 3×10^{-12} molar, respectively).[14] Broken down by proteolytic enzymes into small peptide fragments and amino acids, the pharmacokinetics of eptinezumab is minimally impacted by age, race, or gender. Due to the lack of interaction with the cytochrome P450 (CYP) enzyme system, no CYP-related drug interactions have been reported.[15] Dose adjustments are not expected to be necessary for renal or hepatic impairment.[15,16] Eptinezumab's pharmacodynamic and pharmacokinetic principles are described in Table 1.

Dosage and administration

Eptinezumab is dosed as a 30-min intravenous infusion that must be administered in a healthcare facility.[15] The recommended dose is 100 mg infused every 3 months, but 300 mg every 3 months may be helpful for some patients. Eptinezumab is packaged as 100 mg per 1 mL and must be reconstituted with 100 mL of 0.9% sodium chloride prior to administration. To prepare the 300 mg dose, withdraw a total of 3 mL from three, single-dose 100 mg vials and inject it into a 100 mL bag of 0.9% sodium chloride. Gently invert the solution to mix and do not shake. The infusion should be given through a 0.2 micro or 0.22 micron sterile filter and should be followed with a flush of at least 20 mL of 0.9% sodium chloride. Following reconstitution, it can be kept at room temperature but must be administered within 8 hours.[15]

Table 1. Pharmacokinetics and pharmacodynamics.[15,16]

	Eptinezumab
Time to C_{max}	Immediate
Time to steady state	After the first dose
Half-life	27 days
Volume of distribution (mean)	3.7 L
Bio-availability	100%

Body

The authors performed a systematic search for sources, including articles, abstracts, and poster presentations, published or presented prior to 16 June 2021. The authors searched the National Institute of Health US National Library of Medicine Clinical Trials, PubMed, and Cochrane Library databases by each medication. The search terms included *eptinezumab*, *Vyepti*, and *ALD403*. Additional relevant articles were found through the reference list of these queried articles. All articles and abstracts studying the efficacy and safety of eptinezumab were included. Narrative reviews were excluded.

Clinical trials

Eptinezumab was approved by the FDA on 21 February 2020, based on the results of two randomized controlled trials. Published in 2020, PROMISE-1[17] evaluated eptinezumab in episodic migraines while PROMISE-2[18] evaluated eptinezumab in chronic migraines. Both of these studies met power and maintained a 5% two-sided alpha. Both followed the publication of phase 2b clinical trials on eptinezumab for episodic migraine[11] and chronic migraine prevention.[19] Since eptinezumab's approval, results from the PREVAIL study,[20] which was a 2-year open-label study of quarterly eptinezumab 300 mg for chronic migraine, and the RELIEF study,[21] which assessed the efficacy and safety of eptinezumab 100 mg for an active migraine attack, have been published.

Phase 2b clinical trials. The first phase 2b trial[11] was a randomized, double-blind, placebo-controlled, proof-of-concept, exploratory study. Patients were randomized in a 1:1 ratio to placebo or eptinezumab 1000 mg infusion. At baseline, the placebo group ($n = 82$) had 8.8 migraine days, and the treatment group ($n = 81$) had 8.4 migraine days per 28-day period. Patients receiving eptinezumab 1000 mg experienced a reduction of 5.6 days from baseline to weeks 5–8 compared

to 4.6 days in the placebo group ($p=0.0306$). The reduction remained the same for each group in weeks 9–12 (−5.6 days vs −4.6 days, $p=0.065$). While the remaining endpoints were not tested for statistical significance, eptinezumab reduced migraine episodes, migraine hours, headache days, migraine severity, acute treatment utilization, and improved quality of life indicators across weeks 1–12.[11]

Safety data were similar between the two groups, with mild to moderate adverse effects and no serious events leading to withdrawal.[11] More than 50% in each group experienced an adverse event with three patients experiencing a total of six serious adverse events that were unrelated to the study drug. No patients withdrew due to an adverse event or lack of efficacy. The most common adverse events in the treatment and placebo groups, respectively, were upper respiratory infection (9% vs 7%), urinary tract infection (1% vs 5%), fatigue (4% vs 4%), back pain (4% vs 5%), nausea and vomiting (4% vs 2%), and arthralgia (5% vs 1%). Vital signs, laboratory monitoring, and 12-lead electrocardiogram (ECG) did not reveal any clinically significant differences, although three patients (4%) in the treatment group experienced corrected QT (QTc) prolongation. While 11 patients (14%) in the treatment group potentially formed anti-drug antibodies, there was no impact on efficacy or safety. No patients experienced an infusion reaction.[11]

The second, phase 2b study was a randomized, double-blind, placebo-controlled, dose-finding, single-infusion study in patients with chronic migraine.[19] Patients were randomized 1:1:1:1:1 to receive eptinezumab 10, 30, 100, 300 mg, or placebo. Eptinezumab resulted in ⩾75% decrease in monthly migraine days (MMDs) over weeks 1–12 compared to baseline in 26.8% ($p=0.294$) in the 10 mg group, 28.2% ($p=0.201$) in the 30 mg group, 31.4% ($p=0.072$) in the 100 mg group, and 33.3% ($p=0.033$) of the patients in the 300 mg group compared to 20.7% in the placebo group. The mean number of MMDs at baseline was 16.4, 16.2, 16.9, and 16.5 (10, 30, 100, and 300 mg) versus 16.4 in the placebo group. MMDs were reduced by 6.7 ($p=0.1802$), 7.9 (p=0.0054), 7.7 ($p=0.0178$), and 8.2 days ($p=0.0034$) compared to 5.6 days in the placebo group. Reduction in migraine/headache hours and severe intensity migraines was favorable in the eptinezumab group compared to placebo. A post hoc analysis within the study looked at the migraine-preventive effects beginning the first day following infusion. During the baseline period, 58.7%–60.4% of patients experienced a migraine on any given day. In comparison, 29.3% of patients in the 100 mg group, 26.3% of patients in the 300 mg group, and 48.7% of patients in the placebo group experienced a migraine on day one following the infusion.[19]

Most treatment-emergent adverse events (TEAEs) were mild to moderate and consistent between the different dosing groups.[19] More than half of the patients (56%) included in the safety analysis population ($n=616$) experienced a TEAE with the most common being an upper respiratory infection (6.6% 100 mg, 10.7% 300 mg, and 5.0% placebo) and dizziness (9.8% 100 mg, 1.7% 300 mg, and 7.4% placebo). Sixteen serious TEAEs were reported in 13 patients, but none were related to the study drug. Six patients experienced a hypersensitivity reaction that resolved within 24 hours. Of the 25 patients who withdrew from the study, only 9 withdrew due to lack of efficacy. Laboratory and vital monitoring, including ECG, did not reveal any relevant abnormalities. Anti-eptinezumab antibodies (ADA) formation, with or without neutralizing potential, was not shown to impact efficacy or safety.[19]

PROMISE-1. The Prevention of migraine via intravenous ALD403 safety and efficacy (PROMISE-1)[17] study was a phase 3, parallel-group, double-blind, placebo-controlled, randomized controlled trial conducted between September 2015 and December 2017. The study included patients aged 18–75 years with a diagnosis of episodic migraine according to International Classification of Headache Disorders (ICHD), Second Edition. Acute migraine treatments were limited to ⩽14 days per month. Preventive treatment was not allowed, except for menstrual migraines. Patients were randomly assigned in a 1:1:1:1 ratio to eptinezumab 30, 100, 300 mg, or placebo. During this 60-week study, patients could receive up to four doses at 12-week intervals, but the primary efficacy analysis was based only on the first dose and data through week 12. At week 12, 835 patients (94.0%) remained in the study, and 694 patients (78.2%) remained at week 48.[17]

The mean number of MMDs was approximately 8.6 days during the screening period and was reduced by 3.9 days in the 100 mg group ($p=0.0182$), 4.3 days in the 300 mg group ($p=0.0001$), and 3.2 days in the placebo group over weeks 1–12.[17] The 300 mg group (29.7%, $p=0.00007$) demonstrated significant improvement in ⩾75% reduction in MMD between weeks 1–12 when compared to placebo (16.2%), resulting in a number needed to treat (NNT) of 8. The 100 mg group (22.2%, $p=0.1126$) did not meet significance (NNT 17). According to the predetermined testing hierarchy, the remaining endpoints, including 30 mg dosing group outcomes, could not be considered significant because of this outcome.[17] The study was continued and data at 1 year has been released as abstracts[22,23] and a publication.[24] The study demonstrated sustained or improved outcomes as patients received the second, third, and fourth infusions.

PROMISE-1[17] also evaluated the percentage of patients with a migraine on the day after the first infusion. The average percentage of patients with a migraine on any given day during the baseline period was 30.7%. Only 14.8% in the 100 mg group ($p=0.0312$) and 13.9% in the 300 mg group ($p=0.0159$) experienced a migraine the day following the infusion, compared to 22.5% in the placebo group.[17]

While 530 patients (59.7%) experienced at least one TEAE, only 84 patients receiving the treatment had a study-drug-related TEAE.[17] The most frequent study-drug-related TEAEs were nausea ($n=14$, 1.6%) and fatigue ($n=12$,

1.4%). TEAEs reported by more than 2% in eptinezumab-treated patients also included upper respiratory tract infections. A few patients (17, 1.9%) experienced a serious TEAE but none were determined to be related to the study drug.[17] The rates of TEAE were similar at 12 weeks and 1 year.[22,23] A total of 29 patients (3.3%) experienced a TEAE that led to study withdrawal, six of which were serious and none were related to study treatment.[17] Seven patients who received the study drug had treatment withdrawn due to hypersensitivity, which was mild to moderate and resolved within 24 h. Neither ADAs nor the presence of neutralizing antibodies (NAbs) was determined to impact efficacy or safety.[17]

PROMISE-2. The PROMISE-2[18] study was a phase 3, single-dose, parallel-group, double-blind, randomized placebo-controlled trial conducted between November 2016 and April 2018. The study included patients aged 18–65 years with a diagnosis of chronic migraine according to ICHD, Third Edition. Acute treatments were allowed, including opioids and barbiturates, if used less than 4 days per month. Nearly half of the patients (44.7%) utilized a prophylactic medication while 40.2% (479 patients) had a diagnosis of medication overuse headache. Patients were randomly assigned in a 1:1:1 ratio to eptinezumab 100, 300 mg, or placebo. At week 12, 1049 patients (93.6%) remained in the study, 1000 patients (89.2%) remained at week 24, and 878 patients (78.3%) remained at week 32.[18]

The primary efficacy endpoint was the change from baseline in MMD over weeks 1–12.[18] MMD averaged 16.1 days during the baseline period. The mean number of MMDs was reduced by 7.7 days in the 100 mg group ($p < 0.0001$) and 8.2 days in the 300 mg group ($p < 0.0001$) compared to a reduction of 5.6 days in the placebo group. More patients in the 100 mg group (26.7%, $p = 0.0001$, NNT = 9) and the 300 mg group (33.1%, $p < 0.0001$, NNT = 6) experienced at least a 75% reduction in migraines between weeks 1 and 12 compared to placebo (15.0%). During the screening period, the daily percentage of patients with a migraine was 58%. On day one following treatment, 42.3% in the placebo group had a migraine while only 28.6% in the eptinezumab 100 mg group ($p < 0.0001$) and 27.8% ($p < 0.0001$) in the 300 mg group had a migraine.[18]

The study also concluded that the 100 mg group (−3.3 days, $p < 0.0001$) and the 300 mg group (−3.5 days, $p < 0.001$) reduced acute medication days compared to placebo.[18] Post hoc analysis[25] revealed approximately 50% reduction in triptan and ergotamine acute medication use days. In post hoc results[26] from the phase 2b study on chronic migraine, high triptans users (those using triptans on 10 or more days every 4 weeks) decreased from 18.6% to 3.5% during the first 4 weeks. High triptan users had a better response to eptinezumab in efficacy measures and quality of life measures than the treatment group as a whole.[26] In a subgroup analysis of patients enrolled in PROMISE-2 with a dual diagnosis of medication overuse headache, eptinezumab demonstrated consistent improvement in monthly migraine days compared to placebo over weeks 1–12 (−8.4 days for 100 mg, −3.0 difference from placebo, 95% confidence interval (CI) = −4.56 to −1.52; −8.6 days for 300 mg, −3.2 difference from placebo, 95% CI = −4.66 to −1.78; −5.4 days for placebo) and weeks 13–24 (−9.2 days for 100 mg, −3.4 difference from placebo, 95% CI = −5.03 to −1.85; −9.2 days for 300 mg, −3.4 difference from placebo, 95% CI = −4.99 to −1.87; −5.8 days for placebo).[27] This may further demonstrate that eptinezumab is similarly useful in patients with medication overuse headaches.

While 47.4% of patients experienced at least one TEAE, only 122 patients (11.4%) experienced a TEAE related to the study drug.[18] The most frequent study-drug-related TEAEs were fatigue (1.8% eptinezumab vs <1% placebo) and nausea (1.6% vs <1%). While 10 participants (<1%) experienced a serious TEAE, only one was determined to be related to the drug. A total of six patients had the study drug withdrawn due to hypersensitivity, which were mild to moderate and resolved within 48 h. Neither ADAs nor the presence of NAbs was determined to impact efficacy or safety of eptinezumab.[18]

While each phase 3 study[17,18] demonstrated a significant reduction in MMDs, post hoc analysis of both studies has further dissected the benefit of eptinezumab. There was a consistent reduction in MMDs despite differences in baseline disease characteristics, such as duration of migraine, baseline MMDs, baseline triptan use, and prophylactic medication use, based upon subgroup analysis.[28] Intrinsic factors, such as age, sex, and race, also demonstrated consistent treatment effects.[29] During the first 12 weeks of treatment, more patients (10.8%–16.8%) receiving eptinezumab experienced a migraine-free month compared to placebo (5.1%–9.1%).[30] The percentages of patients experiencing a migraine-free month increased with subsequent doses.[30] In addition, each phase 3 study saw a reduction of nearly 50% (44.1%–47.0%) in acute medication use in patients with at least 10 acute medication use days at baseline.[31] These improvements were consistent with the reductions seen in the phase 2b and the phase 3 chronic migraine studies.[25,26] The studies also looked at the quality of life and found early and sustained relief across several measures.[32–34] Those with worse quality of life at baseline demonstrated greater improvements in these measures.[34]

The difference from placebo in treatment effect on day one was significant for 100 and 300 mg doses in both studies emphasizing the efficacy of eptinezumab starting on day one of therapy and continuing through the study period.[35] In response, RELIEF,[21] a phase 3, parallel-group, double-blind, placebo-controlled, randomized trial, assessed the efficacy and safety of eptinezumab for the treatment of an acute migraine attack. Patients were randomized to eptinezumab 100 mg or placebo infusion within 1–6 h of the qualifying migraine and were not permitted rescue medication 24 h prior to or 2 h following the infusion. The most frequent TEAE was hypersensitivity which was experienced by five patients ($n = 238$) in the eptinezumab group, of which none

were considered serious. Time to headache pain freedom (4.0 h eptinezumab vs 9.0 h placebo, $p < 0.001$) and time to absence of mother bothersome symptom (2.0 h eptinezumab vs 3.0 h placebo, $p < 0.001$) was significant for the eptinezumab group. The eptinezumab group also had a decreased use of rescue medications at 24 hours (31.5% vs 59.9% placebo, $p < 0.001$) and 48 hours (34.9% vs 63.6% placebo, $p < 0.001$). The time to next migraine was 10 days in the eptinezumab group compared to 5 days in the placebo group ($p < 0.001$). These results demonstrate the efficacy of eptinezumab in aborting an acute migraine while simultaneously initiating preventive therapy.[21]

Meanwhile, continued safety and efficacy beyond 12 weeks of therapy was further examined in the PREVAIL trial, a 2-year open-labeled, phase 3 study of patients with chronic migraine who received eptinezumab 300 mg every 12 weeks for up to eight doses.[20,36] Patients enrolled in the trial had a mean of 14.1 MMD days and a mean of 20.3 monthly headache days. The study had a rate of withdrawal due to adverse events of 6.8% (eight patients) with three patients having hypersensitivity. Only 18 patients (14.1%) had a TEAE related to the study drug with hypersensitivity being the most common in this group (five patients, 3.9%). Of the five serious TEAEs, only one was thought to be related to the study drug, which was a grade 2 anaphylaxis reaction with lower lip swelling, hives on the legs, and an itchy scalp occurring after the fifth dose. Twenty-three patients (18%) developed antibodies to eptinezumab during the study. The incidence of ADA was the highest at 24 weeks (21/120 patients, 17.5%) then declined despite continued dosing to 0% at week 104. A few patients (7%, 9/128) developed NAbs during the study period. The frequency of NAbs increased over the study period, peaking at week 12 and then decreasing to zero at week 72.

Efficacy in the PREVAIL trial was based on patient-reported outcomes such as change in Migraine Disability Assessment (MIDAS) score, patient-identified most bothersome symptom (MBS) associated with migraine, Patient Global Impression of Change (PGIC), and 6-item Headache Impact Test (HIT-6). At baseline, the mean MIDAS total score was 56.8 (standard deviation (SD) = 52.0) and decreased starting with the first assessment at 12 weeks (mean = 20, SD = 40.2). This was maintained through week 104 (mean = 22.0, SD = 58.9). Patients saw improvement in their MBS beginning at week 4. At the last measure of MBS at week 48, 75% of patients reported "much improved" or "very much improved" severity of their MBS. Similar reductions and sustained improvement were noted in the PGIC and HIT-6. It is notable that this open-label study had no comparator and only measured patient-reported outcomes, thus creating a risk for bias.[20] The other previously discussed studies primarily looked at MMD as an efficacy measure.

The above trials[17,18,20,21] presented several limitations, including a lack of participant diversity (Table 2) which makes generalizability difficult. PROMISE-1[17] and PROMISE-2[18] also set the primary efficacy endpoint at 12 weeks of therapy which only analyzed the first infusion. Interim analysis from the continuation of PROMISE-1 demonstrated sustained or improved efficacy over 1 year for patients with episodic migraine receiving 100 mg (−4.5 day, −0.76 difference from placebo 95% CI = −1.40 to −0.11) and 300 mg (−4.8 day, −1.02 difference from placebo 95% CI = −1.66 to −0.37).[24] The ⩾75% and ⩾50% response rates also demonstrated sustained or improved outcomes through the end of the fourth infusion.[22,23] A continuation study of the PROMISE-2 trial did find continued reduction in MMD at 24 weeks (−8.2 days for 100 mg, difference from placebo −1.98, 95% CI = −2.94 to −1.01; −8.8 day in the 300 mg group, difference from placebo −2.65, 95% CI = −3.62 to −1.68; −6.2 days in placebo).[37]

Table 2. Baseline characteristics.

	% White	% Female	Mean age (years)
Dodick et al.[11]	80.5	81.5	38.8
Dodick et al.[19]	89.0	87.0	37.0
PROMISE-1[17]	83.8	84.3	39.8
PROMISE-2[18]	91.0	88.2	40.5
PREVAIL[20]	95.3	85.2	41.5
RELIEF[21]	86.0	84.0	44.5

On-going clinical trials. Eptinezumab has several ongoing clinical trials.[38] DELIVER (NCT04418765) is a phase 3, double-blind, parallel-group, placebo-controlled, randomized clinical trial that intends to determine the efficacy and safety of eptinezumab for patients with migraines refractory to prior treatment. A similar clinical trial is looking at the impact of eptinezumab in patients with medication overuse headache (SUNLIGHT NCT04772742). ALLEVIATE (NCT04688775) is a phase 3, placebo-controlled trial looking at the safety and efficacy of eptinezumab in patients with episodic cluster headaches. A clinical trial (NCT04336449) assessing the pharmacokinetics and pharmacodynamics of eptinezumab in healthy Japanese subjects was completed in 2020 with the publication of results still pending while a clinical trial (NCT04537429) looking at the pharmacokinetics of eptinezumab in children and adolescents is also ongoing.[38]

Conclusion

Eptinezumab 100 and 300 mg resulted in early, sustained efficacy in migraine prevention. Eptinezumab resulted in a numerical large reduction in monthly migraine days in PROMISE-2[18] but has not been compared to the other CGRP monoclonal antibodies. At week 12, each eptinezumab phase 3 study[17,18] had approximately 94% of patients remaining in the study. Both PROMISE-1[17] and PREVAIL[36] documented the fourth treatment at week 48, with 78.2%–87.5% of patients remaining in the study. Conversely, oral migraine-preventive agents have demonstrated poor

adherence, due to poor efficacy and tolerability.[7,39] Low rates of withdrawal and high rates of continuation in the eptinezumab studies are hopeful for real-world adherence to the medication, likely encouraged by the quarterly dosing regimen along with good tolerability and quick onset of efficacy.

In PROMISE-1[17] and PROMISE-2,[18] the majority (47.4%–59.7%) of patients experienced a TEAE, but most were unrelated to the study drug. The most frequent eptinezumab-related TEAEs were fatigue and nausea, each occurring in less <2% of patients. Between the two studies, only 12 patients were withdrawn for a hypersensitivity reaction, all of which were mild or moderate and resolved in a timely manner. While the high rates of continuation and the favorable side effect profile bode well for eptinezumab, the other monoclonal antibodies have had more side effects reported once made available to the public. For example, erenumab now carries a warning for potentially serious constipation and new-onset or worsening of hypertension, based on post-marketing surveillance.[40] Eptinezumab, like the other CGRP monoclonal antibodies, excluded patients with vascular disease (including cardiovascular disease or cerebrovascular disease), neurological disease, hypertension, and ECG abnormalities from its clinical trials.[17,18] As a result, patients with known cardiovascular or neurological diseases should be closely monitored while taking eptinezumab.

The quick onset of eptinezumab will likely contribute to its place in therapy, especially among the other monoclonal antibodies. As an infusion, eptinezumab has immediate bioavailability and therefore has an almost immediate impact. PROMISE-1 and PROMISE-2 demonstrated improvement beginning on day one post-infusion[35,41] while RELIEF[21] demonstrated that eptinezumab could simultaneously abort a migraine and initiate a patient on prophylactic therapy. The early onset of efficacy could also help combat medication overuse as demonstrated by the reduction in acute medication use and triptan use.

Conversely, eptinezumab is more costly per dose and requires time for supervised administration, compared to the other CGRP monoclonal antibodies that are available as autoinjectors for self-administration. Eptinezumab wholesale acquisition cost is estimated at US$1495.00 for a 100-mg dose.[42] Since the medication is administered as an infusion in a healthcare facility, there are indirect costs to consider as well. As of June 2021, the manufacturer currently does not offer a patient assistance program but instead offers a commercial copay assistance program for qualified patients.[43] Eptinezumab's manufacturer offers the medication for as little as US$5 per infusion every 3 months with a maximum annual benefit of US$4000.[43] With copay assistance, the cost of eptinezumab is comparable to the other available monoclonal antibodies. Despite the higher cost per dose, eptinezumab's quarterly administration results in a yearly cost (US$5980.00 for 4–100 mg doses) which is similar to the other CGRP monoclonal antibodies. To directly compare, erenumab costs US$638.77 per monthly injection, regardless of dose, resulting in nearly US$8000 per year in 2021.[44] The wholesale acquisition price of onabotulinumtoxin A 200 units (the recommended dose is 155 units quarterly for chronic migraine) is currently estimated at US$1244, which also does not include indirect or administration costs.[45,46] Notably, cost-effective analyses comparing erenumb, onabotulinumtoxin A, and placebo have concluded that erenumab is cost-effective in patients with chronic migraines but is less cost-effective for those with episodic migraines.[47] With similar cost and efficacy for erenumab and eptinezumab, one can consider both treatments evenly appropriate based on cost.

No head-to-head studies have been completed comparing various CGRP monoclonal antibodies. One network meta-analysis conducted by Wang et al.[48] attempted to compare MMD and TEAEs for the four available monoclonal antibodies. Comparison to placebo yielded significant differences in patient MMD for each of the agents. When comparing various agents to one another, no significant differences were found in efficacy. Ranking of each agent revealed fremanezumab had the highest probability of being ranked first to reduce monthly migraine days (MMD = −2.19 compared with placebo, 95% credibility interval (CrI) = −3.15 to −1.25) with eptinezumab (MMD = −1.43 compared with placebo, 95% CrI = −2.59 to −0.36) being ranked fourth overall. In safety, TEAEs were more frequent in the galcanezumab group compared to placebo (relative risk (RR) = 1.11, 95% CrI = 1.01 to 1.22). Galcanezumab was ranked first among agents most likely to cause TEAE. Eptinezumab was ranked third overall (RR = 1.03, 95% CrI = 0.87 to 1.20, compared with placebo) in most likely to cause TEAE. It is notable that these comparisons include both episodic and chronic migraine patients and each medication at various doses.[48]

For episodic migraines, the 2012 American Academy of Neurology (AAN)/American Headache Society (AHS) guidelines on episodic migraine prevention in adults recommended that antiepileptic drugs (valproic acid and topiramate), beta-blockers (metoprolol, propranolol, timolol, atenolol, and nadolol), and antidepressants (amitriptyline and venlafaxine) can be offered for migraine prevention, and the triptans (frovatriptan, naratriptan, and zolmitriptan) can be offered for short-term prevention of menstrually associated migraine.[49] The efficacy of these agents is similar to or less than that of the CGRP monoclonal antibodies based on individual trial outcomes, not comparative studies.[49] Poor adherence is also common among these agents, likely secondary to side effects.[7] Because these agents are oral with available generics, cost to consumers is generally low. Topiramate numerically decreases total migraine days less than that of eptinezumab, but in the absence of head-to-head studies, no conclusions can be made regarding comparative efficacy.[50,51]

While the cost and infusion time of eptinezumab may deter utilization, eptinezumab's quick onset and 100% bioavailability could be beneficial for those with severe, episodic, or chronic migraine patients. The intravenous infusion of

eptinezumab gives an additional route of administration for patients while the quick onset provides immediate relief. Eptinezumab has demonstrated efficacy, especially for those with chronic migraine and high utilization of acute medications, similar to the other agents in its class. Eptinezumab resulted in numerically stronger improvement in chronic migraineurs than in episodic migraineurs, making it more cost-effective in the chronic migraine population. This provides a safe option for a potentially harder-to-treat population. Furthermore, the low incidence of side effects, the most common being nausea and fatigue, could enable long-term tolerability for patients. Considering these factors, eptinezumab's place in therapy is likely that of salvage therapy after failure of oral, non-specific preventive migraine therapies due to cost. In lieu of major differences between efficacy, safety, and cost among CGRP monoclonal antibodies, eptinezumab may be reserved for those who are resistant to self-injections or patients wanting immediate migraine relief with initiation of migraine prevention.

Author contributions

The authors have met the criteria of authorship and agree to the conclusions of the study. K.W.M. made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data. Drafted the article or revised it critically for important intellectual content. Approved the version to be published. Participated sufficiently in the work to take public responsibility for appropriate portions of the content. K.R.J. made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data. Drafted the article or revised it critically for important intellectual content. Approved the version to be published. Participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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