Clinical Efficacy and Safety of Prophylactic Drugs for Chronic Migraine

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Abstract: Chronic migraine (CM) is a prevalent disease that induces neurological symptoms. CM burdens the life qualities of patients with comorbidities, including cardiovascular and psychiatric disorders. Monoclonal antibody Eptinezumab, targeting Calcitonin gene-related peptide (CGRP), is a prophylactic treatment for CM. The efficacy and safety of Eptinezumab are confirmed in 6 clinical studies, as 83.3% of patients reported improved life quality after 104 weeks. Other commonly used prophylactic drugs, incorporating antiepileptic drugs, beta-blockers, and triptans, have also established their efficacy and safety in clinical conditions. This paper analyses the efficacy and safety of Eptinezumab and compares it to other prophylactic drugs.

1. Introduction

As a pervasive neurologic disorder and the second leading cause of disability worldwide, chronic migraine (CM) impacts 1% to 2% of the global population while provoking many comorbidities [1]. Cardiovascular diseases, including stroke, transient ischemic attack, and coronary heart disease were reported. Psychiatric disorders such as depression, bipolar disorder, and suicide ideation, possibly induced by reduced serotonin synthesis, were linked with CM patients [2]. Increased frequency of CM episodes escalates related comorbidities, resulting in continuous disabilities [3]. Patients experience headaches, nausea, vomiting, and sensitivity to environmental stimuli in CM episodes, limiting their normal function and life quality [1].

Innervated by the unmyelinated C fibers, the trigeminal nerve promotes afferent pain information that gives rise to CM, also deposit neuropeptide calcitonin gene-related peptide (CGRP) [4]. CGRP is recognized to have a vasodilatory effect. The stimulation of CGRP to mast cells, followed by the neuron sensitizing agents, induces neurogenic inflammation and vasodilation. Moreover, the trigeminal nerve stimulates the trigeminal nucleus caudalis (TNC), delivering the signal to the posterior thalamic area (PTA), the centre of environmental stimuli and pain integration. CGRP is heavily presented in PTA and elevates hypersensitivity to stimuli such as light in CM patients [5]. CGRP is defined as a target in CM treatment due to its vital role in pain transduction.

Preventive treatments of CM are considered because of their reoccurring nature. Several drug classes are included. Monoclonal antibody CGRP inhibitor Eptinezumab (ALD403) inhibits the CGRP signalling pathway. Initially synthesized in rabbits, Eptinezumab is fully humanized and exhibits weak FcγR binding to avoid immunogenicity and cytotoxicity [6]. List in the level A pharmaceuticals with documented efficacy, beta-blockers, antiepileptic drugs, and triptans also showed effectiveness in CM control [7]. The lack of specific prophylactic drugs designed for CM, in addition to the lack of animal and human disease models, burdens the efficacy prediction [8]. This review focus on the clinical studies of Eptinezumab and prophylactic drugs to discuss their clinical efficacy and safety.

2. Different phase Clinical studies of Eptinezumab

2.1 Phase 1b

Safety and efficacy assessments were conducted on patients who received one IV doses of ALD403 or placebo. Efficacy was measured by the frequency of migraine days. The reduction in the frequency of migraine days was -5.6 for the treatment group, in contrast to -4.6 for the placebo (p=0·0306) [9].

2.2 Phase 2

Eptinezumab was administrated through single IV infusions in chronic migraine patients (n=616, mixed gender). The results demonstrated 33.3%, 31.4%, 28.2%, 26.8% and 20.7% ≥75% migraine responder rates over 12 weeks, provided by Eptinezumab dose of 300, 100, 30, 10 mg and placebo, respectively (p = 0.033, 0.072, 0.201, 0.294 respective to 300, 100, 30, 10 mg doses). Both Eptinezumab doses of 300 and 100 mg showed significantly superior responder rates over placebo. The adverse effects rates of Eptinezumab treatment groups were similar to the placebo group. Therefore, this study demonstrated the satisfying effectiveness and safety of Eptinezumab [10].

2.3 Phase 3

Reduced mean monthly migraine days (MMDs) of 30 mg, 100 mg, 300 mg dosage over 12 weeks indicated significant decreases (30 mg, -4.0, p=0.046; 100 mg, -3.9, p = 0.0182; 300 mg, -4.3, p=0.0001; placebo, -3.2). ≥50% migraine responder rates were 50.2, 49.8, 56.3 and 37.4 were induced by 30 mg, 100 mg, 300 mg, and placebo respectively. 300 mg dose group obtained highest ≥75% migraine responder rate (29.7%), followed by 30 mg (24.7%) and 100 mg (22.2%) compared to placebo (16.2%) [11].

Migraine patients (n=1072) in PROMISE-2 study experienced MMDs of -8.2, -7.7 and -5.6 induced by Eptinezumab dose of 300, 100mg and placebo, respectively (p<0.0001 for 300 and 100 mg). The ≥50% migraine responder rates over 12 weeks were 57.6, 61.7, and 39.3 for 300, 100 mg, and placebo (p<0.0001 for 300 and 100 mg). Both dosage groups induced a significant reduction in acute medication days in 12 weeks (100 mg, -3.3 days; 300 mg, -3.5 days; placebo, -1.2 days; p <0.0001). Patients who received a single dose of Eptinezumab experienced maintaining migraine preventive effects throughout 12 weeks. This study demonstrated the meaningful efficacy of Eptinezumab [12].

The RELIEF study assessed the effect of Eptinezumab on pain and symptom relief. Two hours after IV administration, most bothersome symptoms were reduced by 55.5% and 35.8%, respectively to Eptinezumab and placebo groups (p<0.001) [14]. This result was consistent with the PREVAIL study. By week 48 of the PREVAIL study, 75% of patients experienced “much improved” or “very much improved” from bothersome migraine symptoms, such as sensitivity to stimuli, pain, and nausea. At the end of the 104 weeks, patients with severe disability were reduced to 20.8%, while approximately 60% reported little to no disability. 83.3% of patients voted “much improved” to describe the effect on their life quality. The findings aligned with the PROMISE studies, where patients experienced significantly reduced monthly migraine days after administering 100 mg or 300 mg of Eptinezumab. This study defined satisfactory long-term improvement in life quality [13].

Table.1. Clinical studies of Eptinezumab (ALD403)

Phase	Patient number	Dose	Study design	Efficacy	Reference
1b	163	ALD403 1000 mg or placebo	randomized, double-blind, placebo-controlled	Reduce in MMD over 12 weeks: -5.6 for treatment group; -4.6 for placebo; ≥ 75% responders over 12 weeks: 24% for treatment group; 9% for placebo	[9]
2	665	ALD403 10 mg, 30 mg, 100 mg, 300 mg, or placebo	randomized, double-blind, placebo-controlled	≥ 75% responders over 12 weeks: 33.3% for 300 mg; 31.4% for 100 mg; 28.2% for 30 mg; 26.8 % for 10 mg	[10]
3 (Promise 1)	888	ALD403 30 mg, 100 mg, 300 mg, or placebo	randomized, double-blind, placebo-controlled	Reduce in MMD: -4.0 for 30 mg; -3.9 for 100 mg; -4.3 for 300 mg; ≥ 75% responders: 30% for 30 mg 30.8% for 100 mg; 31.5% for 300 mg	[11]
3 (Promise 2)	1072	ALD403 100 mg, 300 mg, or placebo	randomized, double-blind, placebo-controlled	Reduce in MMD: -7.7 for 100 mg; -8.2 for 300 mg; ≥ 75% responders: 30.9% for 100 mg; 36.9% for 300 mg	[12]
3 (PREVAIL)	128	ALD403 300 mg	Open-label	Reduce in disability score: -36.7 in the end of 104 weeks; % Of patients with improved life quality: 83.3% after 104 weeks	[13]
3 (RELIEF)	485	ALD403 100 mg or placebo	randomized, double-blind, placebo-controlled	Pain relief 2 hours after injection: 23.5% for treatment group and 12.0% for placebo; % Patients used rescue medication: 31.5% for treatment group and 59.9% for placebo	[14]

3. The efficacy of Sodium valproate for CM

The efficacy of the antiepileptic drug sodium valproate was established in the past few decades. The frequency of migraine attacks, the pain severity, and the attack durations was effectively decreased in contrast to the placebo group in a cross-over comparison clinical trial conducted with 32 patients [15]. The results were partly aligned with another cross-over study completed by 34 patients, where

the average migraine days of sodium valproate treated groups were significantly reduced, contrasting the placebo group (p=0.018). Patients with a serum level above 50 mg/l had reduced average migraine days from 6.1 to 3.5 days. 50% of patients (17/34) experienced 50% or fewer migraine days reduction. 12% (4/34) patients were responders to reduce 75% to 100% migraine. The duration, intensity, and the number of coexisting tension-type headache days showed a reduction, but non-significant compared with placebo [16]. In a clinical trial conducted by Yurekli et al., sodium valproate reduced the maximum pain level and the pain frequency parameters in the first month significantly. The general pain parameter was decreased at the end of three months from 6.7 to 2.7 (P=0.03 compared to placebo) [17].

A clinical trial with a larger patient population (n=88) to assess the efficacy of 800 mg sodium valproate were conducted by Sarchielli et al. The rate of ≥50% responder rate after three months was 22% greater in sodium valproate group compared with placebo. Sodium valproate was used to treat medication-overuse headaches in this study. Sodium valproate demonstrated a short-term carryover effect; therefore, long-term drug treatment was needed [18].

Sodium valproate was used in targeting specific populations, such as pediatric migraine prophylaxis. 72% of patients (41/57) in the treatment group reported ≥50% migraine frequency. 56% of sodium valproate treated patients experienced a relief of headache severity. Responders for pain duration reduction, complete ceasing of headache attack, and improved rescue medication responses were 52%, 21%, and 61%, respectively. The therapeutic effects of sodium valproate were compared with propranolol, a beta-blocker that obtained efficacy in migraine prophylaxis. Percentage of patients in the propranolol group that experienced ≥50% reduced migraine frequency, severity, attack duration, complete ceasing of headache attack, and improved rescue medication responses were 69%, 64%, 53%, 17%, and 67%, respectively. Hence propranolol showed minimal difference in therapeutic effects compared with sodium valproate [19]. This result contrasted with the study by Dakhale et al., where propranolol reduced significantly greater severity of headache than sodium valproate [20].

4. The controversial effectiveness of propranolol for CM

Propranolol is a regularly used medication for migraine management. The indication of propranolol was originally for cardiovascular diseases treatment, followed by the discovery of its use in treating other diseases such as hypertension, non-cardiovascular conditions, including migraine and anxiety. Its efficacy in migraine prevention was established in the past decades [21]. Two double-blind, single-crossover studies measured the patients' preference between propranolol and placebo to indicate efficacy [22, 23]. Significantly more patients preferred propranolol over placebo due to the reduction in headache frequency. However, no difference was shown in drug consumption [23].

The effects of propranolol were confirmed in another double-blind cross-over trial. Propranolol produced a significant improvement in the frequency of migraine, pain intensity, and total duration of attacks. However, the propranolol group showed minimal difference in mean attack durations and reduction of bedridden days compared to the placebo group [24].

The efficacy of a daily dose of 160 mg long-acting propranolol was investigated. Long-acting propranolol significantly decreased monthly migraine frequency in 12 weeks from 6.11± 0.93 to 3.15 ± 0.77 compared to placebo [25]. Contrastingly, propranolol failed to significantly reduce migraine attacks and the mean duration of migraine compared with placebo [26].

5. The preventive effect of frovatriptan

Frovatriptan is a triptan that obtains agonist effects on 5-HT receptors. The clinical efficacy of 2.5 mg triptan was investigated in three studies with 2676 patients. It was reported that frovatriptan significantly reduced pain response 2 hours after administration, with a two-fold effect over placebo. The 24-hour headache recurrence was lowered, and the mean recurrence time was longer in the frovatriptan group. The satisfaction rate of patients was 44% to 51% compared to 17% to 30% for placebo, indicating a significant improvement in life quality in the short term. Frovatriptan

demonstrated a rapid onset of action around 2 hours after administration. For most patients, the relief effect of frovatriptan could last 24 hours [27].

Frovatriptan is utilized to manage menstrual migraine. The efficacy of frovatriptan dose daily (QD) and twice a day (BID) was assessed. Both regimens significantly reduced the frequency of headache, pain severity, and headache duration, while the effect of BID was superior to QD. Associated symptoms such as nausea and vomiting were reduced significantly for both groups. The functional impairment in patients was improved. 66% to 86% of patients rated positive treatment satisfaction, which was enormously superior to placebo, where 16% to 32% of patients rated positive [28]. This result was aligned with a later study assessing the short-term preventive effect of frovatriptan in women with menstrual migraine. The occurrence of headache, pain severity and functional impairment was significantly reduced in both QD and BID groups. Rescue medication use and the number of associated symptoms reported were lowered [29].

Frovatriptan provided short-term prevention in patients lacking sustained acute treatment efficacy. The headache-free perimenstrual period was significantly higher for frovatriptan BID and QD than placebo. The associated symptoms and rescue medication usage was reduced significantly. This study confirmed the preventive effect of frovatriptan during the 6-day treatment period in 28 days cycle [30].

6. The Safety of different prophylactic drugs

Among six clinical trials of Eptinezumab (ALD403), most adverse effects were not drug-related [9-14]. Most adverse effects reported obtained mild to moderate severity. The main adverse event that led to patient withdrawal was hypersensitivity (11 in PROMISE 1, 6 in PROMISE 2, 3 in PREVAIL). The majority of the hypersensitivity reactions were below moderate and were cured in one day. Frequent adverse events included hypertension, upper respiratory tract infection, dizziness, nausea, and nasopharyngitis. One patient in PREVAIL study experienced a severe blurred version. Most mild to severe adverse events were resolved in one day [9-14].

Two patients experienced serious drug-related adverse events among the six clinical trials [12, 13]. One patient in PREVAIL study experienced a grade 2 anaphylaxis event. The symptoms included erythema, pruritus, nasal congestion, and hives on the body, described as an allergic reaction [13]. In the PROMISE 2 study, one patient reported worsening migrainous visual aura 126 days after receiving the second dosage of 300 mg Eptinezumab. The serious adverse event lasted four days, with the underlining cause remaining unknown [12]. No relationship was established between Eptinezumab doses and adverse events. No life-threatening or fatal adverse events occurred. The development of tolerability was also acceptable, as only 18% of patients developed anti-drug antibodies (ADA), and 7% of patients developed antibodies with neutralizing potential (NAbs). No impact was observed from ADA and NAbs [13]. Therefore, Eptinezumab established satisfying safety with good tolerability and an acceptable adverse event rate.

Four clinical studies indicated low adverse effect rates for sodium valproate with no serious adverse events. Six patients discontinued the study, potentially due to negative side effects. 2% of patients in the study of Yurekli et al. experienced somnolence, tremor, impotence, and hair loss, which resolved after termination of sodium valproate administration. The adverse event rate for propranolol was as well low. No serious side effects were observed. Main adverse events included tiredness, fatigue, and gastric dysfunction such as pain and diarrhoea [15-18].

The safety and tolerability of 2.5 mg frovatriptan were assessed in the short-term and long-term use of 12 months, where 1% of patients chose to withdraw due to adverse effects for both short-term and placebo groups. Due to the deficiency of tolerability, 5% of patients discontinued the long-term study. Overall, frovatriptan provided good tolerability. 90% of adverse effects were reported to have a mild to moderate severity. Frequent adverse effects include dizziness, headache, nausea, fatigue, and somnolence. The long-term adverse effects aligned with short-term observations, as most adverse effects had mild to moderate severity [31]. The clinical trial of S. D. Silberstein et al. reported that most adverse events occurred 48 hours after administration. Most adverse events were mild to moderate.

Table.2. Adverse effects outcomes

Medication	Adverse effect rate	Severity	Main adversity effect	Reference
ALD403	57% in treatment group; 52% in placebo group	Mostly mild to moderate; No relevant severe adverse effects	Upper respiratory tract infection, urinary tract infection, back pain, arthralgia, nausea, vomiting	[9]
ALD403	56% in treatment group; 56.2% in placebo group. Drug-related adverse effects: 16.4% in treatment group; 14% in placebo	Mostly mild to moderate; 2.4% of patients experienced severe adverse effects; not related to drug	Upper respiratory tract infection, dizziness, nausea, nasopharyngitis, sinusitis, bronchitis, migraine	[10]
ALD403	59.7% in treatment group; 58.4% in placebo group. Drug-related adverse effects: 12.6% in treatment group; 8.6% in placebo	Severe adverse effects: 1.7% in treatment group; 2.7% in placebo group; not related to drug	Upper respiratory tract infection, nasopharyngitis, sinusitis, dizziness, nausea, back pain, cough, fatigue	[11]
ALD403	47.4% in treatment group; 43.5% in placebo group. Drug-related adverse effects: 13.2% in treatment group; 7.9% in placebo	Severe adverse effects: <1% in treatment group; <1% in placebo group; 1 drug-related serious adverse effect	Upper respiratory tract infection, nasopharyngitis, fatigue, migraine, sinusitis, urinary tract infection	[12]
ALD403	71.1% in ALD 300 mg group; Drug-related adverse effects: 14.1% in ALD 300 mg group	Severe adverse effects: 10.2% in treatment group; not related to drug. Serious adverse effects: 3.9% in treatment group; 1 drug-related serious adverse effect	Hypersensitivity, fatigue, anaphylactic reaction, back pain, constipation, dermatitis, hypotension	[13]
ALD403	Drug-related adverse effects: 10.9% of the treatment group; 10.3% of the placebo group	Mostly mild to moderate; No relevant serious adverse effects	Hypersensitivity, fatigue, anaphylactic reaction, back pain, constipation, dermatitis	[14]
sodium valproate	18.8% in the treatment period; 6% in the placebo period	No serious side effects; 2 withdrawals due to sodium valproate adverse effects	Dyspepsia, nausea, mild weariness	[15]
sodium valproate	33% in the treatment period; 16% in the placebo period	No serious side effects; 4 withdrawals during sodium valproate period	Nausea, dyspepsia, tiredness, increase appetite, weight gain	[16]
sodium valproate	2% in the treatment group	No serious side effects	Somnolence, tremor, impotence, hair loss	[17]

sodium valproate	37% of the treatment group; 45% of the placebo group	No serious side effects	Nausea, vomiting, worsening headache, diarrhoea, weight gain, hair loss	[18]
Propranolol	4.8% to 9% of the treatment group; 4.8% to 16.3% of the placebo group	No serious side effects	Tiredness. Dyspepsia, diarrhoea, insomnia, depression, dizziness	[25]
Propranolol	24.4% of the treatment group; 9.1% of the placebo group	No serious side effects	Reduced heart rate, depression, gastric pain, diarrhoea	[26]
Propranolol	9% in the treatment period; 9% in the placebo period	No serious side effects	Fatigue, polyuria, low back pain	[24]
frovatriptan	47% of the treatment group; 34% of the placebo group	No serious side effects	headache, dizziness, nausea, fatigue, somnolence and parethesias	[27]
frovatriptan	78% to 87% of adverse effects were reported in 48 hours after dosing	No serious side effects	Headache, nausea, dizziness, nasopharyngitis fatigue	[29]
frovatriptan	59% in BID group; 70% in DD and placebo group. Drug-related adverse effects: 24% in BID group; 32% in QD group; 19% in placebo group	2 serious adverse events; not drug-related	upper respiratory tract infection, nausea and dizziness	[30]

The clinical trials of Eptinezumab demonstrated good clinical efficacy, safety, and tolerability. Both 100 mg and 300 mg of Eptinezumab was confirmed to provide stable long-term efficacy. The majority of patients reported having an improved life quality [13]. Two drug-related serious adverse effects were raised in clinical trials. Most adverse events were below moderate and healed in 24 hours. The population that participated in the Eptinezumab trials was large. However, there is a lack of research in specific populations, such as children and chronic migraine caused by other reasons.

Prophylactic drugs have been used in CM treatment in the last decades. Effective prophylactic drugs included sodium valproate, propranolol, and frovatriptan. They demonstrated their efficacy by reducing the occurrence of headache, pain severity, and headache duration, although some research showed contrasting results [26]. Serious side effects were rare in prophylactic CM treatments. Most of the adverse events were mild to moderate as well. However, this finding is limited by the range of literature selection. Many of the selected clinical trials were conducted in the late 2000s with a small patient population.

Due to its long history in CM management, prophylactic drugs provided complete efficacy and safety profiles for specific patient populations, including children, women with migraine associated with menstruation, and patients with medicine-overuse-induced headaches.

Although prophylactic drugs obtained satisfying efficacy and safety profile, the effects are primarily short-term. Daily or twice-a-day dosing is required to maintain its effect. Eptinezumab can provide migraine relief for three months after each dose, improving patient compliance. However, the

administration route of IV injection may decrease the drug compliance compared with oral administration of prophylactic drugs.

7. Conclusions

Eptinezumab is a preventative medication designed explicitly for chronic migraine. The safety and efficacy of Eptinezumab were analysed with its clinical trials. The efficacy and safety profile of prophylactic drugs sodium valproate, propranolol, and frovatriptan were also investigated. Both Eptinezumab and prophylactic drugs obtained good safety and efficacy. Eptinezumab provided better long-term pain relief than prophylactic drugs, while lacking special population studies. Prophylactic drugs were used to actuate migraine relief and short-term headache prevention. Daily administration is required, whereas Eptinezumab only requires one dose every three months. The administration route of prophylactic drugs may be easier for patients to follow. The number of literature selections limits this review. More modern clinical trials with higher patient numbers could be selected in future research. The selection of prophylactic drugs could be more comprehensive, including other common migraine treatments such as antidepressants and ACE inhibitors.

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