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Fremanezumab as CGRP Antagonist and its Role in Migraine

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Abstract

Migraine is a disease that is still often experienced and can reduce community productivity. The prevalence of migraine occurs in 4% - 9% in men and 11% - 25% in women. Migraine therapy is divided into preventative therapy and curative therapy. Migraine prevention therapy has recently become a new development in the world of health. The drug that has just been approved by the FDA is Fremanezumab. Fremanezumab is a CGRP antagonist, its research has entered phase III where this drug can be used in more patients. Some guidelines recommend the use of this drug as a preventative measure for migraine. In this review it can be concluded that fremanezumab can be used to prevent migraines and at least the occurrence of side effects.

Keywords: Fremanezumab, calcitonin-gene related peptide, Migraine, CGRP antagonist

1.0 INTRODUCTION

Migraine is a brain disease that often occurs that involves abnormal neuronal tissue activity and affects levels within the central also peripheral nerves (Puledda, et al., 2017). Migraine is a headache that has quite a lot of prevalence and can reduce the productivity of sufferers. In a study showed 4.5% of the population in Europe experienced headaches at slightest 10 days per month or more (Welch & Goadsby, 2002). Migraine is generally described as a feeling of severe and periodic pulsations in an area of the head (Bahri & Zulfazli, 2015). Migraines are more common in female sex than men (18% and 6%) with a greater prevalence in the age range of 35-45 years. Common causes are caused by factors such as stress, weather, emotional, hormones, fatigue including lack of sleep and excessive sleep (Brasher, 2007). Data from a study shows that 1% of the world's populace has migraine (Natoli, et al., 2010).

Recurrent migraines are characterized by migraine sufferers who experience pain in 0 to 14 days per month, and chronic migraines are characterized by at least 15 days' headache occurred per month. Based on the ICHD-2 criteria, defining chronic migraine as a cerebral pain at least 15 days per month for minimum 3 months, where at least 8 days meets the criteria for migraine without the aura also the treatment, occurs in patients with at slightest five previous pain attacks which were also not caused by other cause disorders and there was no excessive use of drugs (Katsaraya, et al., 2011). Patients who experience chronic migraine can experience changes in metabolism, then there is hyperexcitability to to the focal sensory system, and focal sensitization.

Patients with migraine that utilize exorbitant combination of analgesics will have less metabolism in the cortex of orbitofrontal than patients that use only one analgesic. A study about PET *scans* of 10 patients with chronic migraine and consist an increasing of metabolism in the pons also the dexter temporal cortex compared with all brain metabolism. The areas of decreasing metabolism are occurred in several areas including the parietal, somatosensory cortex, medial frontal and in the bilateral caudate of nucleus. The activity of certain brain stem can indicate that excitation of cortical is increased in person with chronic migraine. Researchers concluded that high excitation from cortical area can make chronic migraine patients vulnerable to the triggers and clarify the high recurrence of migraine attacks (Matthew, et al., 2004; Burstein & Jakubowski, 2005; Matthew, 2011).

Patients who experience recurrent migraines can turn into chronic migraines. Annually, there are 2.5% of patients experiencing chronic migraines who had recurrent migraines. Not all patients can experience this change, this is highly influenced by several risk factors. Risk factors can be partitioned into two classifications: things that can be changed (obesity, depression in healthy lifestyles, use of drugs) and things that cannot be changed (head injury, level of education and socio-economic life of the patient, age, female gender) (Bigal & Lipton, 2006; Lipton, 2006; Bigal, et al., 2008).

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2.0 CGRP IN MIGRAINE

CGRP is a 37-aminoneuropeptide which is also a neurotransmitter, there are two structures namely alpha-CGRP and beta-CGRP. Alpha-CGRP can be found in the focal and peripheral nervous system, while beta-CGRP found in enteric nervous system. CGRP is disseminated in the amygdala striatum, hypothalamus, thalamus and brain stem (Russel, et al., 2014; Goodsby, et al., 2017). In a study in which CGRP was injected into humans then headaches and migraine symptoms were recorded. The results of this study stated that CGRP can trigger migraines (p 0.003) and delayed headache (p 0.001) (Hansen, et al., 2010).

Migraine can affect the cortical and subcortical parts of the brain by modulating sensory information. Migraine has a process that occurs in the periaqueductal gray (PAG) area. After a migraine causes cortical changes, changes in brainstem activity or both, then the trigeminal system is activated. When the trigeminal system is activated, CGRP will be released from nerve endings in the cranium (Bigal, et al., 2015). Besides CGRP triggers migraines, CGRP also has an effect on the sensitization of the trigeminal part which can then be a risk factor for an increase in the frequency of headaches. This can predispose to migraine development from recurrent migraine to chronic migraine (Bigal, et al., 2013; Iyengar, et al., 2017; Kopruzinski, et al., 2017).

CGRP is synthesized by nerve damage. After being synthesized, CGRP is stored inside vesicles in the sensory nerve. After a process of neuronal depolarization, CGRP is released through exocytosis. CGRP follows up on two channels, the CGRP-receptor canonical complex and the transmembrane protein (RAMP 1). RAMP 1 have the function to encourage the cell-surface expression of reseptor complex and also usual for the CGRP binding, but excessive expression can cause migraines. The second CGRP receptor is the amylin receptor (AMY1). Trigeminal ganglion is found as a site where the greatest CGRP expressed (Goodsby, et al., 2017).

Trigeminal ganglion has a significant role in the process of migraine or primary headaches. CGRP play a role in this regard that expression of CGRP in trigeminal can form A and C-fibers. CGRP fibers stored in the trigeminalvascular system, in the trigeminal ganglia cell body. Trigeminal nerve activation causes the release of CGRP and this makes the advancement of migraine preventive drugs that block the activity of CGRP (Durham, 2006; Edvinsson, 2017).

3.0 FREMANEZUMAB

This drug is a specific IgG2a monoclonal antibody in both CGRP isoforms in humans. Fremanezumab is able to bind CGRP then it will interfere with CGRP in signaling through the receptor, indicated by inhibition of cAMP release. Fremanezumab has local vasodilation inhibitory activity caused by CGRP after treatment using capsaicin. This drug has peripheral activity (Zeller, et al., 2008; Walter & Bigal, 2015; Melo-Carrillo, et al., 2017).

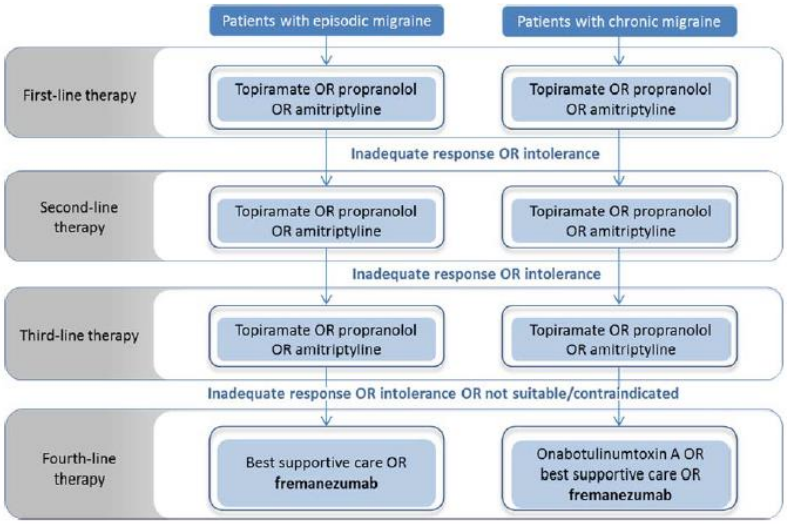

Figure 1. Guidelines for Migraine Prevention (NICE, 2019)

Fremanezumab as a migraine prevention drug was accepted by the Food and Drug Administration (FDA) in September 2018 under license from Teva Pharmaceuticals with the trademark AJOVY. Fremanezumab is a drug that is completely a monoclonal antibody in humans (IgG2a) which later binds to CGRP and can later bind to the receptors so that CGRP levels will be reduced so that migraine does not occur. The recommended dose is 225 mg once per month or 675 mg once every three months (given 3 injections with 225 mg per dose), given in subcutan dosage form. Avoid inject fremanezumab to the same location that has been previously injected (Hoy, 2018).

One study mentioned that fremanezumab inhibits Aδ neurons instead of neurons in C fibers. In the results of the study there was a reduction in the percentage of neurons that were shown to be activated by cortical spreading depression (CSD). This could be information that fremanezumab has an action on Aδ neurons in migraine prevention. However, it has no effect on dorsal horn neurons, so it can be said that it might not have the same effect in all patients who have migraines (Melo-Carrillo, et al., 2017). Subcutaneous use of fremanezumab results in the maximum time fremanezumab reaches its maximum level of 507 days. Steady state time is achieved in approximately 6 months either fremanezumab with a dose 225 mg per month or 675 mg every 3 months. Volume distribution of this drug was recorded at 6 liters. Fremanezumab has a fairly long half-life of 31 days and a clearance of 0.141 L/day. Metabolism of this drug occurs degradation through enzymatic proteolysis into peptides and amino acids. This drug is not metabolized by cytochrome P450 enzyme so that this drug is not affected by cytochrome P450 agonist or antagonist. Fremanezumab also did not find any interaction with acute migraine treatment such as analgesics, ergots and triptans. (Anon., 2019; Anon., 2019; Cohen-Barak, et al., 2018).

The use of fremanezumab in patients who have greater body weight is associated with an increase in central clearance and volume of distribution. The pharmacokinetics of fremanezumab are also known to be unchanged with differences in age, albumin levels, renal function, sex, injection location and also the use of analgesic drugs (Fiedler-Kelly, et al., 2019). Fremanezumab is known to be safe and tolerable, with no serious side effects and also significant changes in vital signs, laboratory data and ECG data. Fremanezumab also mentioned no difference in side effects compared to placebo including the incidence of pruritus and pain at the injection site. In recurrent migraine patients, who received fremanezumab had a consistent change in pain threshold every day compared to placebo (p 0.011) (VanderPluym, et al., 2018). Side effects mentioned in several studies were injection site pain (24% vs 22% placebo), hardening at the injection site (17% vs 13% placebo) and erythema at the injection site (16% vs 12% placebo). Also mentioned also fremanezumab causes respiratory infections (4%) and nasopharyngitis (4%) (Robblee & VanderPluym, 2019). The good from Fremanezumab (Bigal, et al., 2018):

1. Fast onset. Fremanezumab for recurrent migraine occurs after 1 day of subcutaneous use, this is also the same for intravenous eptinezumab.
2. Good clinical response, with a decrease in acute drug consumption and improved quality of life in patients.
3. Not bound by their previous therapeutic failure.
4. Have good tolerance and safety of side effects, almost the same as placebo.

Difference between Fremanezumab and other anti-CGRP (Bigal, et al., 2018) :

1. Fremanezumab has a route through subcutaneous, whereas eptinezumab via intravenous.
2. Fremanezumab usage intervals can be done every month or every three months.
3. Fremanezumab can be used as monotherapy or it can also be an additional therapy. Both of these have the same efficacy.

4.0 CLINICAL TRIALS

Several studies have been conducted to prove the efficacy of fremanezumab and also find out what side effects occur due to the use of this drug.

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Table 1. Clinical research of fremanezumab

Author	Year	Methods	Results
Silberstein, et al.	2017	RCT phase III. Patients who have migraine with chronic (≥ 15 days and ≥ 8 days per month) receive fremanezumab subcutaneously as every 3 months (single dose of 675 mg, placebo at weeks 4 and 8), and fremanezumab subcutaneously every month (675 mg at baseline and 225 mg at week 4 and 8). Then the average change from baseline to the duration of the subject experiencing migraine were noted.	Of a total of 1130 subjects, a total of 376 were given subcutaneous fremanezumab every 3 months, 379 mg every month and 375 place to. The percentage of migraine pain reduction was 38% in the fremanezumab group every 3 months, 41% in the fremanezumab group every month and 18% in the placebo group (p <0.001 both compared with placebo). Abnormal liver function occurred in 5 patients in the fremanezumab group and 3 in the placebo group. Fremanezumab can be used for migraine prevention.
Ferrari, et al.	2019	RCT double-blind, Phase IIIb conducted in 104 centers (hospitals, health centers, research institutions and clinical practices in the country of mostly Europe and United States). Subjects were 18-70 years old with recurrent and chronic migraines. Subjects were divided into 3 groups, quarterly fremanezumab subcutan (675 mg in the first month, 2nd and 3 months' placebo), monthly subcutaneous fremanezumab (repeated migraine subjects received 225 mg for the first month, while chronic migraine subjects received 675 mg fot the first month, then for month 2 and 3 both groups received 225 mg), then the placebo group. The change after 12 week treatment in mean migraine pain day were noted.	A total of 838 migraine subjects (329 recurrent migraines and 509 chronic migraines) and 279 placebo. The quarterly subcutaneous fremanezumab group was 276, the monthly fremanezumab was 283. The reduction from baseline in the monthly group was greater than the placebo group and the quarter group. Side effects were experienced by 1% in the placebo group and <1% in the quarterly fremanezumab group and 1% in the monthly fremanezumab group. From this research, fremanezumab results are effective and can be well tolerated to prevent migraines.
Silberstein, et al.	2019	RCT in migraine patients with high frequency given treatment with fremanezumab 225 mg or 675 mg and also placebo every 28 days within 3 months. Changes in the number of migraines noted in days for 3 months of the trial.	A total of 297 subjects were divided into 3 groups. The subject group given fremanezumab (225 mg and 675 mg) could reduce migraine days compared with the placebo group during the first week (p <0.001), the second week (p <0.001) and also the third week (p 0.003). Migraine symptoms have succeeded decrease in week 1, 2 and 3. From this study it can be concluded that fremanezumab

			can provide a rapid preventive response.
Dodick, et al	2018	Double blind RCTs at 123 centers in 9 countries. Subjects were divided into 3 groups (receiving fremanezumab every month, fremanezumab per 3 months and placebo). In the monthly fremanezumab group, subjects received subcutaneously as much as 225 mg at baseline, weeks 4 and 8. The fremanezumab group every 3 months received 674 mg at baseline then placebo at weeks 4 and 8. Results were evaluated in 12 week.	From baseline to week 12 there was a decrease in pain duration from 8.9 days to 4.9 days in the monthly fremanezumab group, 9.2 days to 5.3 days in the single dose fremanezumab group and in the placebo group from 9.1 days to 6.5 days. Side effects include erythema, diarrhea, anxiety and depression. The fremanezumab group significantly reduced migraine pain ($p < 0.001$) compared with placebo.

4.1 Pros and cons of CGRP antagonist

Fremanezumab can cause mild pain at the injection site, pruritus and erythema. The use of fremanezumab through intravenous injection requires that it be done by a doctor and also requires patients to regularly visit a doctor. But this can be facilitated because this drug has a long half-life so it makes it easier for patients to visit the doctor once a month (Deen, et al., 2017). On the other side, fremanezumab can prevent migraines compared to placebo. In the phase III study, fremanezumab reduced 3.4% compared to placebo by 2.2% from the baseline. The pros and cons outlined above concluded that the benefits of CGRP antagonist therapy especially fremanezumab is greater than the losses obtained (Deen, et al., 2017).

5.0 CONCLUSION

CGRP can play a role in triggering migraines. CGRP antagonists can reduce recurrence from recurring migraines. Fremanezumab as one of the CGRP antagonist group drugs works by blocking CGRP and preventing it from binding to its receptors. Further research on this subject is needed in various human races which may have different results.

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