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Aimovig serving as a miracle drug for chronic migraine – A clinical Review

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ABSTRACT:

Migraine being a very serious issue unaddressed by most of the patient assuming it as a normal headache is leading to the chronic conditions of the individual. These conditions are increasing across the globe and the awareness within our communities need to be taken care of as it is a complex neurological disorder which is related to several CNS systems such as sensorics and motoric, cognitive, affective and autonomous systems is categorised as migraine. The calcitonin gene related peptide receptor (CGRP) is the receptor of calcitonin family which also includes amylin, adrenomedullin and calcitonin receptors. Among these CGRP receptors play a major role in migraine but its exact role is yet to be analysed. Already existing treatments such as Triptans showed high agonist activity at serotonin receptors but not every triptan has the affinity at the receptors. However, Patients mentioned that the response of the body towards this triptans is poor and others may have headache recurrence and chest syndromes. Aimovig a miracle drug came to existence showing its effectiveness more appropriately and significantly by pre-clinical and clinical studies proving to show the statistical analysis of 70mg of aimovig shows p value of <0.001 and of 140mg p value of <0.001 which are similar. The secondary outcomes of the results are the % of participants with at least 50% of reduction in monthly migraine days (which differ from each patient). Aimovig is proving to show less adverse events associated irrespective of the other factors and showed more effectiveness in reducing the migraine condition and improving the quality of life of the patients.

Keywords: Aimovig, calcitonin gene related peptide receptor, headache, Migraine.

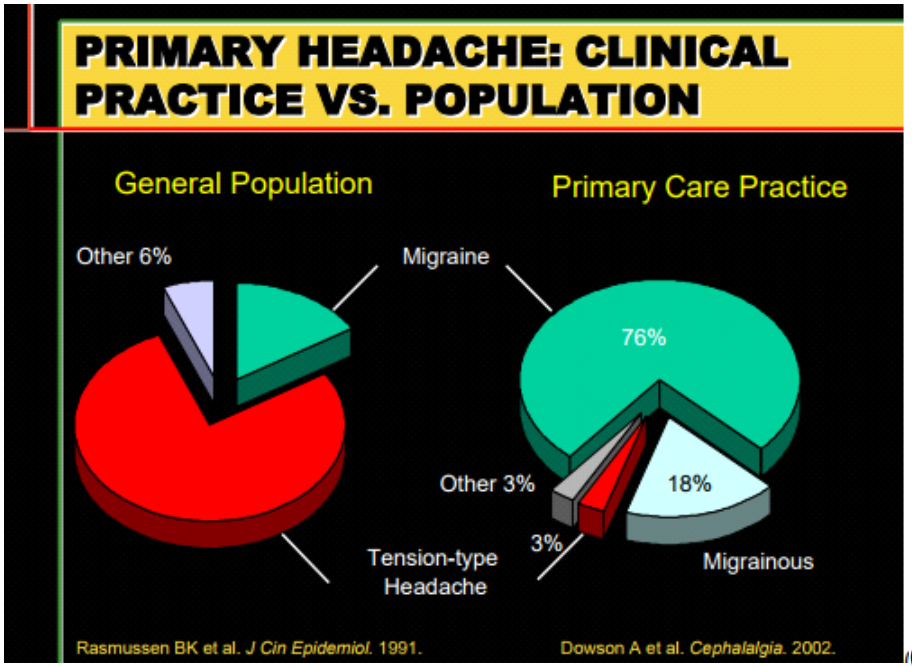
INTRODUCTION:

A complex neurological disorder which is related to several CNS systems such as sensorics and motoric, cognitive, affective and autonomous systems is categorised as migraine. This disorder is often accompanied by sensitivity to light, sound and smell (Schipper, R. Gantenbein and S. Sandor, 2016). Migraine is classified into 3 different types such as migraine with aura, without aura and migraine aura without headache. Migraine with aura is that which gives indications to the person before the migraine actually starts. Migraine without aura is the type where it does not give any kind of warning sign before it starts and this is the common type of migraine that is identified by practitioners. Migraine aura without headache is the type where the person experiences all aura attacks other than headache. Migraine usually begins in adulthood. The main symptoms of migraine is usually intense headache on one side of the head, in some cases it may

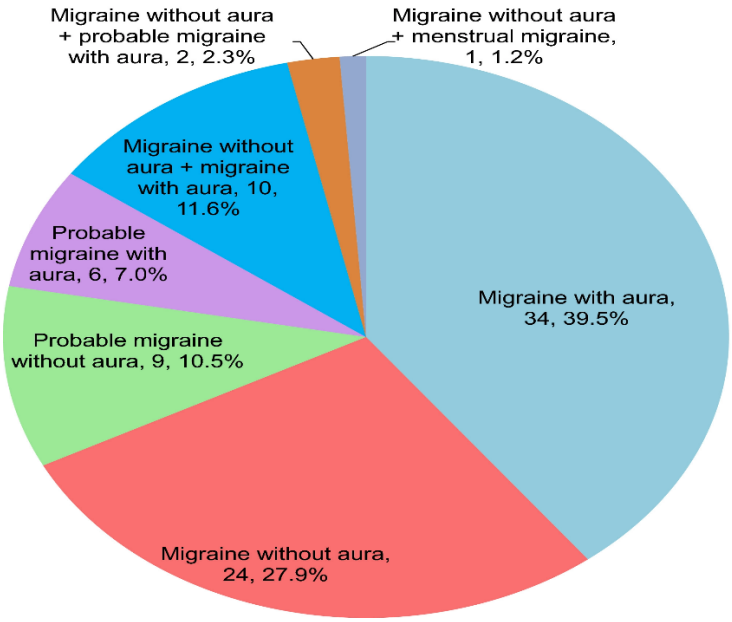
effect both the sides of the head and thereby spreads to face and neck. There are additional symptoms of migraine such as nausea, vomiting, sweating, poor concentration, feeling very hot or very cool, abdominal pain and dialarhoea. Migraine with aura have symptoms such as visual problems where the person loses his sight from certain minute to months. There are many causes for migraine such as hormonal, emotional, physical, dietary, environmental and medicinal factors (nhs.uk, 2019). To treat migraine of short mild attacks of migraine, analgesics together with antiemetics are prescribed. And for the severe attacks triptans were suggested (Göbel et al., 2014).

EPIDEOMOLOGY:

In the year 1991 the population with migraine seems to be 18% and the tension type headaches are 76% as mentioned in the image given below and when it comes to the year of 2002 migraine is estimated to be 76% and 6% is tension type headache and 18% is the chance to get migraine (Facebook.com, 2019).



(Facebook.com, 2019) (Bebbington, 2001)



(Yeh,2018)

PATHOPHYSIOLOGY:

The calcitonin gene related peptide receptor (CGRP) is the receptor of calcitonin family which also includes amylin, adrenomedullin and calcitonin receptors. Among these CGRP receptors play a major role in migraine but its exact role is yet to be analysed. CGRP receptors stimulate neurotransmitters or neuro peptides that will increase intravenous signals in the brain and there by lead to severe headache and pining of brain with needles sensation when nociceptive signals within trigemini vascular system are released (Aimovighcp.com, 2019).

NEED FOR NEW THERAPIES:

Triptans showed high agonist activity at serotonin receptors but not every triptan has the affinity at the receptors. In animal studies when anesthetised animals were injected with the triptans they showed decrease in arteriovenous anastomotic fraction of carotid blood flow. In the blood vessels they caused contraction and this effected more on cranial arteries. Patients also mentioned that the response of the body towards this triptans is poor and others may have headache recurrence and chest syndromes. Because the contraction of blood vessels and chest syndromes seemed very difficult to manage researchers have followed their studies to develop new drugs for migraine (Saxena and Tfelt-Hansen, 2001).

PRE-CLINICAL STUDIES:

1)In the animal studies first the generation of aimovig 334 antibody is performed in Xenomouse with soluble CGRP receptor protein as antigen. (Shi et al., 2015).

2) Cell line and cell culture Human neuroblastoma cells endogenously expresses human CGRP receptor were isolated from 14-year girl with neuroepithelioma and chronic migraine and cultured (Shi et al., 2015).

3) Membrane preparation and binding affinity studies of aimovig on human, rabbit, mouse and dog CGRP receptors (Shi et al., 2015)

RESULTS OF PRECLINICAL STUDIES:

In preclinical studies show that CGRP receptors are used as positive control and aimovig 334 as the test drug. CGRP receptors showed the agonistic activity with IC 50 value of 3.9 +/- 20nM with maximum inhibitory effect of 93.3% Aimovig 334 did not show any agonistic activity even at high concentrations (10micro M) but displayed the antagonist activity.

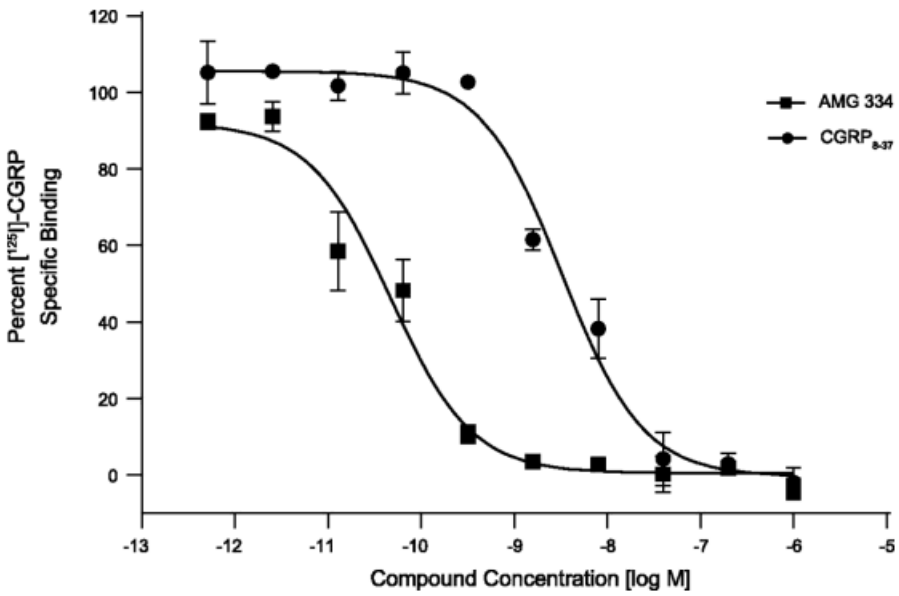


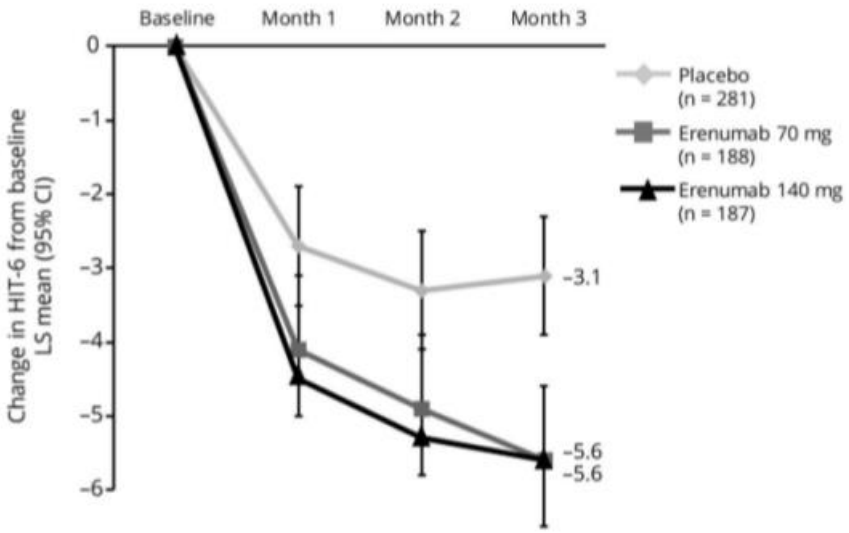
fig 1 represents the inhibitory effect between the CGRP that is used as the positive control and aimovig 334 that is used as the test drug in mouse (Shi et al., 2015).

CLINICAL TRIALS:

These clinical studies were performed in North America and other places (69 study sites) with 667 adults who were selected based on the days of headache and migraine conditions with more than 15 days of headache per month and among which more than 8 days were migraine days. This study was double blinded, placebo-controlled study with patients having chronic migraine selected randomly (70/140mg monthly) given subcutaneously as injection. The study was done for 3months (phase 2 study). The results were observed for headache impact test, migraine disability assessment test, pain interference and migraine specific HRQoL (migraine specific quality of life questionnaire). (Lipton et al., 2019)

RESULTS OF CLINICAL TRIALS:

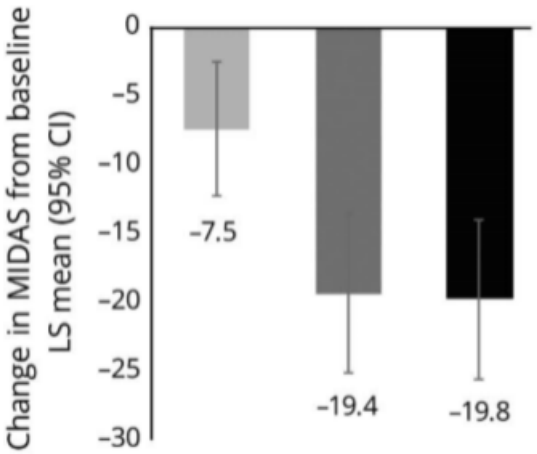
Headache impact test:



(Lipton et al., 2019)

Fig 2 illustrates the result of headache impact for 3months and it showed that erenumab of 140mg showed maximum inhibitory effect towards the CGRP receptors and reveal the patients from migraine headache impact.

MIGRANE DISABILITY ASSESSMENT TEST:

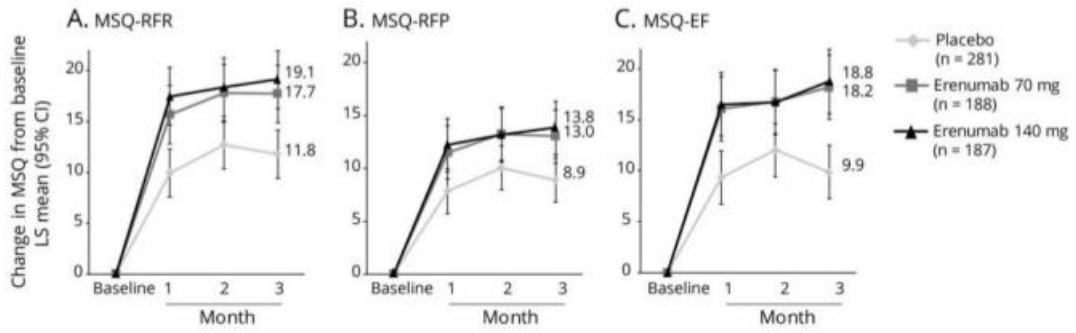


(Lipton et al., 2019)

Fig 3 illustrates the migraine disability assessment test that is performed for 3 months period of clinical study and showed that the erenumab at 140mg (the black bar in the graph) people were much improved in their activities were the migraine stress was decreased of 5 days of migraine related disability.

MIGRANE SPECIFIC QUESTIONNAIRE (MSQ) QUALITY OF LIFE:

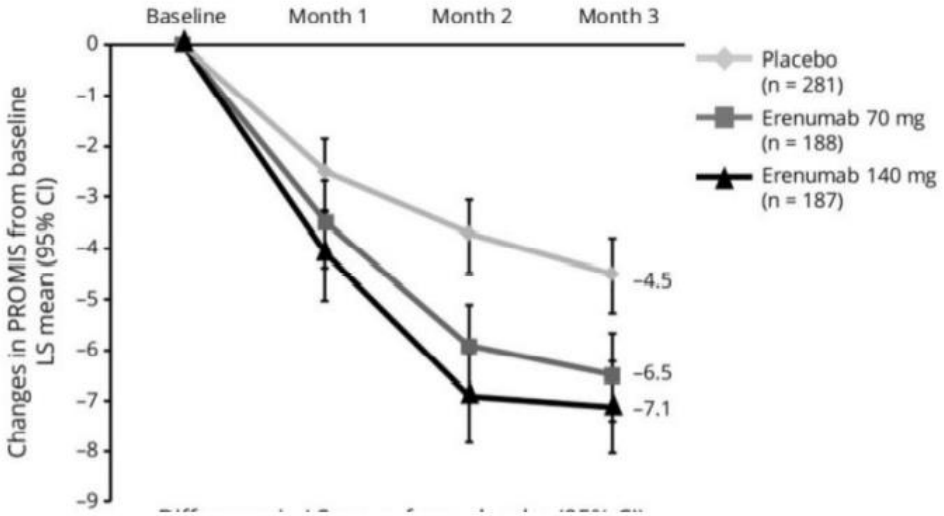
In this study 3 aspects were mainly analysed to checked, MSQ-RFR (role of functional restrictive), MSQ-RFP (role of functional preventive) and MSQ-EF (emotional functioning).



(Lipton et al., 2019)

Fig 3 illustrates the results of the migraine specific questionnaire to improve the quality of life in regards to restriction, prevention and emotional function of the person.

PATIENT- REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM(PROMIS) SCORES:



(Lipton et al., 2019)

REAL LIFE CASE STUDY:

Naomi a lady from Northampton is a business manager for largest acquiring banks in the world. She has been diagnosed with migraine at the age of 14 years. when she started taking aimovig recommended at national migraine centre started her dose at 70mg where is experienced the relief of pain on the same day but the severe migraine attack was continuing in just less pain condition. On the next visit to the hospital the doctor suggested her for 140mg and she states that the dose was really a life changing medication in her life and observed that she was no longer suffering from daily pain (National Migraine Centre, 2019).

DISCUSSION:

Chronic Migraine is the severe disability disorder that is associated with many conditions like sensitivity to light, sound and smell and as well with the release of neurotransmitters and neuropeptides (Buse et al., 2012). In the preclinical studies mentioned above first generation of aimovig 334 antibody is done in the xenomouse and the studies were prolonged in rabbit, dog and mice. The graph mentioned is only the effect on the mouse and not on the other animals used in the study. The effect of the drug might be different in the rabbit, dog and mice. The generation of Aimovig 334 might not be as appropriate as that of xenomouse in rabbit, dog, mice and human cell line and there by the result can be different to each other. Potency of the drug on cynomolgus monkey was similar to human cell line with IC 50 of 5.7nM but the potency on dog, rabbit and rat receptors was significantly reduced (> 5000 folds). So, the results mentioned are not so appropriate with all the animal studies and few studies arose some events as well. In the clinical studies that have been mentioned above the study is performed in 69 study sites irrespective of region that includes Canada, Czechia, Denmark, Finland, Germany, Norway, Poland, Sweden, United Kingdom and United States. The potency and the efficacy of the drug might not be effective when compared with each other though the overall study shows that the drug was potent at 140mg dose. Enrolment of patients with the age starting from 18 years to 65 years were the condition of the patient in 18 years is different from the condition of the patient in 65years. The recruitment in the clinical studies were of both the sexes so the drug's effectiveness may differ in the female and male patients. The recruitment also shows that the female patients were 82.8% and male patients were 17.2%. The patients that are recruited for clinical trials also have the patients who have received prior migraine prophylactic medication was 73.8% and patients who did not have any prior medication was only 26.2%. In such cases patients already exposed to the prior medication and among them 32.1% have shown success rate which also have impact on the aimovig treatment. The results were not calculated with difference in environment, health allergies, condition of patient, tolerability of the drug etc., results might not be same when calculated separately. with medication the over use status of the drug can also have impact over Aimovig use in the clinical trials. This criterion is measured as >15 days of simple analgesics, triptans, ergots and combination therapy which impact on the effectiveness. The monthly migraine days for each person will be different and their condition or the stage of migraine differs, but the calculation was done without any separation. The statistical analysis of 70mg of aimovig shows p value of <0.001 and of 140mg p value of <0.001 which are similar. The secondary outcomes of the results are the % of participants with at least 50% of reduction in monthly migraine days (which differ from each patient). The adverse events that are observed with Aimovig are categorised into 5 grades, grade 1 is the adverse events with mild asymptomatic or mild symptoms, grade 2 are the events with moderate, minimal, local/non-intervention indications, limiting age appropriate activities of daily living, grade 3 are the events associated with severe or medically significant but not immediately life threatening , hospitalization or prolongation of hospitalization indicated, limited self-care, grade 4 are the life threatening consequences and urgent intervention indications, grade 5 are death related to adverse events. All the adverse events were observed in grade 2 and 3. (Clinicaltrials.gov, 2019).

LIMITATIONS OF THE DRUG:

Aimovig is the drug that cannot be used by pregnancy women or the women that are planning to carry a baby as the drug shows the permeability to placental barrier which effects the foetus.

CONCLUSION:

Aimovig is the drug that showed less adverse events associated irrespective of the other factors and showed more effectiveness in reducing the migraine condition and improving the quality of life of the patients. The drug should be even more researched to decrease the adverse effects and improve the reduction of the pain and migraine levels in patients.

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