Research Article ISSN 2639-846X

Anesthesia & Pain Research

Treatment of Chronic Migraine with Erenumab Alone or as an Add on Therapy: A Real-World Observational Study

Guy P Boudreau*

Clinique des céphalées de Montréal. 3875 rue Saint-Urbain bureau 420, Montréal Qc. H2W 1V1, Canada.

***Correspondence:**
Guy Pierre Boudreau, Clinique des céphalées de Montréal. 3875 rue Saint-Urbain bureau 420, Montréal Qc. H2W 1V1, Canada.

Received: 30 April 2020; **Accepted:** 29 May 2020

Citation: Guy P Boudreau. Treatment of Chronic Migraine with Erenumab Alone or as an Add on Therapy: A Real-World Observational Study. Anesth Pain Res. 2020; 4(1): 1-4.

ABSTRACT

Objectives: *Chronic migraineurs having failed more than 3 preventive drugs were treated with Erenumab alone or as an add on therapy, we assessed the frequency of monthly migraine days, the value of an add on therapy, and all adverse events.*

Method: *After signing an informed consent, patients were clustered in 3 categories. Group I: Erenumab alone. (No botox cohort). Group II: Botulinum Toxin A (Botox), with Erenumab. (Botox cohort). Group III: oral preventive drug with Erenumab. (No Botox cohort).*

Results: *Evaluation was after the 4 th injection session. A total of 158 patients were involved. 90 (13%) patients in the Botox cohort. 83 (15%) patients in the no Botox cohort. 53pts/158 (34%) obtained no improvement, 36pts/158 (23%) obtained a reduction of the intensity only, 69pts/158 (43%) reduced the frequency of their monthly migraine days. 57% of patients failed the primary end point. 69 patients reduced their migraine frequency: in group I: 16patients (26%), In group II, 45 patients (65%), and group III, 11 patients (15%) reduced their monthly migraine days by 5-7 days. 72 adverse events were experienced mostly with the 140 mg dose. The most frequent were: constipation 34%, fatigue 19%, itching 7.5%, muscle cramps 6.3%, increased headache 4.4%, rhinitis 4.4%, injection site discomfort 3.7%, lack of energy 3.1%.*

Conclusion: *The add on of Erenumab to a preventive therapy is more effective than Erenumab alone, Botulinum toxin A with Erenumab was the most effective combination.*

Clinical Trial Identifier: NCT04152434.

Keywords
Chronic migraine, Erenumab, Botulinum toxin.

Introduction
Botulinum toxin Type A and Topiramate, were currently the only drugs approved for the preventive treatment of chronic migraine. There is a high unmet need for new preventive therapy for chronic migraine patients that have failed current preventive therapies.

Erenumab (Aimovig), reduced monthly migraine days and increased the likelihood of achieving 50% or more in monthly improvement in migraine days [1-4].

Objective
In a real world setting and in a prospective observational way we evaluated, the efficacy and tolerability of Erenumab in patients suffering of chronic migraine, that had failed more than 3 preventive drugs. The primary objective, was the reduction in the frequency of monthly migraine days. The secondary objective, was to asses if the add on of Erenumab to another preventive therapy was of value, and to assess all adverse events related to the use of Erenumab.

Method
Chronic migraineurs with migraine 15-30 days per month at baseline with or without an actual preventive drug, who failed more than 3 preventive drugs previously, were clustered in

3 groups. All patients were naïve to monoclonal anti CGRP antibodies. All patients signed an informed consent, were given headache calendars. Patients received sub- cutaneous Erenumab (Aimovig) 70 or 140mg. monthly, the only monoclonal anti CGRP antibody available in Canada at the time of this study. Failure of Erenumab was defined as no improvement in the frequency of monthly migraine days and/ or the presence of adverse events that mandated to stop the drug.

Group I

On no preventive therapy at the start of Erenumab, (no Botox cohort)

Group II

On Botulinum Toxin type A prior to the add on therapy with Erenumab (Botox cohort).

Group III

On an oral preventive therapy prior to the add on therapy with Erenumab (no Botox cohort). Patients with an oral preventive therapy were on topiramate, metoprolol, flunarizine, and pizotifen. All patients were selected at one site, at ''la Clinique des Céphalées de Montréal'' from December 2018 to March 2019. Subjects were selected during their clinical consultations. All Patients consented to participate in the study. Analysis of the results was with the data on headache calendars (Figure 1). Previously failed preventive treatments before participating in this study, was considered if the patients had no reduction in the frequency of their monthly migraine days compared to baseline, or had adverse events that mandated to stop the treatment. The study treatment lasted 9 months. All subjects were Caucasian, francophone, 95% were female, with a mean age of 45 years, suffering of chronic migraine, with migraine days from 15-30 days per month. The previous duration of chronic migraine was between 5 to 18 year.

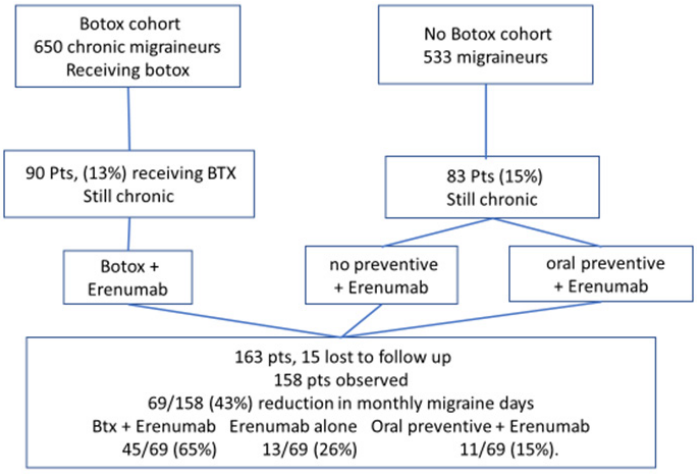

Figure 1: Patient selection and outcome.

Results

Patients were evaluated after the 4th injection session. One hundred and seventy-three patients were eligible, 15 were lost to follow up. A total of 158 chronic migraineurs were involved in this study. 118 patients (75%), received Erenumab 140 mg, they had high frequency monthly migraine days., and 40 patients (25%) received 70 mg they were chronic migraineurs but less frequently affected by monthly migraine days.

In the Botox cohort, of 650 patients receiving Botulinum Toxin A every 3 months, 90 (13%) patients were responding to Botox but still had more than 15 migraine days per month, were eligible. In the no Botox cohort, of 533 patients followed at our clinic for migraine and not receiving Botulinum Toxin A, 83 (15%) patients suffering of chronic migraine were eligible. From all cohorts; 53pts/158 (34%) obtained no improvement in the frequency and intensity of their migraines, 36pts/158 (23%) obtained a reduction in intensity of their migraines only, 69pts/158 (43%) reduced the frequency of their monthly migraine days. Fifty seven percent of patients failed the primary end point.

The primary objective being the reduction of monthly migraine days, of these 69 patients, in the Erenumab alone, group I: 16patients (26%) reduced their monthly migraine days. In the Botox plus Erenumab, group II, 45 patients (65%), and in the oral preventive plus Erenumab, group III, 11 patients (15%) reduced the frequency of their monthly migraine days by 5-7 days. In group II and III all patients became episodic, in group I, 25% stayed chronic but 75% became episodic (Figure 2, and Table 1).

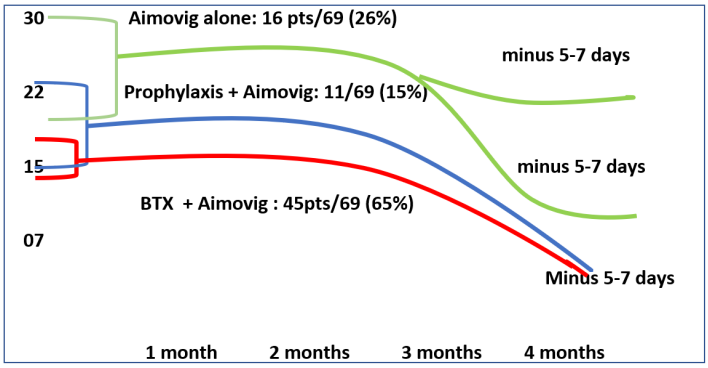

Figure 2: Cohorts that reduced monthly headache days compared to baseline Headache days.

Reduced frequency of migraine	Reduced intensity of migraine only	No improvement of migraine
69pts/158 (43%)	36pts/158 (23%)	53pts/158 (34%)

Table 1: Primary objective: reduction in monthly migraine days, all cohorts at 4 months.

Seventy-two adverse events were experienced during the 9 months of treatment, 56 events with the 140 mg. dose (118 patients), and 16 events with the 70 mg. dose (40 patients) (Table 2). All adverse events were continuous except for muscle cramps, headache, and rhinitis, those events were transient. Injection site discomfort was occasional. Patients were asked: ''do you have any adverse events'', from injection 1 through injection 5, some patients had more than 1 adverse event. Constipation was the most frequent and troublesome adverse evnt. Some patients stopped because of numerous adverse events; up to 4 adverse events for some

patients. Patients that stopped because of adverse events, did not have satisfying improvement from Erenumab. The adverse events inciting patients to stop Erenumab was fatigue, muscle ache, increased headache, and severe constipation.

Constipation	55 patients	34%
Fatigue	31 patients	19%
Itching	12 patients	7.5%
Muscle cramps	10 patients	6.3%
Increased headache	7 patients	4.4%
Rhinitis	7 patients	4.4%
Injection site discomfort	6 patients	3.7%
Lack of energy	5 patients	3.1%
Sweating	3 patients	1.8%
Depressive mood	3 patients	1.8%
Weight gain	2 patients	1.2%
Anxiety	2 patients	1.2%
Dry skin	2 patients	1.2%
insomnia	1 patient	0.6%
Joint pain	1 patient	0.6%
Tremor	1 patient	0.6%
Dry mouth	1 patient	0.6%
Rectal bleed	1 patient	0.6%
Nausea	1 patient	0.6%
Heaviness of limbs	1 patient	0.6%

Table 2: Rate of adverse events related to Erenumab.

Discussion

Antibodies against Calcitonin Gene Related Peptide (CGRP) or against the CGRP receptor have been tested as prophylactic treatment of episodic and chronic migraine [1-4]. All monoclonal antibodies showed a significant reduction in their primary endpoint, mean change from baseline in monthly migraine days [3]. The data from 20 studies provides consistent evidence for the role of CGRP in the prophylactic treatment of migraine [4].

As for Erenumab, 609 subjects were enrolled to the OLE study and 451 (74%) completed the study [1]. Only the responders continued for the duration ensuring a positive bias for efficacy. A numerically greater benefit was observed with Erenumab 140 mg. compared with 70 mg. dose at 40- and 52-weeks completers. At 12 weeks, both 70 mg. and 140 mg. erenumab dose group dropped -6.6 days from baseline. The 50% responder rates for reduction in monthly migraine days were 40% for the 70 mg. and 41% for the 140mg. dose at 12 weeks in the RCT [1].

In this observational prospective study, all patients were kept in the study for 5 months or longer. The patients that reduced the frequency of their monthly migraine days by 5-7 days at the 4th week, were rare compared to the results of the published clinical trials [1-4]. In this cohort of chronic migraineurs, patients started improving after the fourth month (4th injection). A study assessing the percentage of patients with chronic migraine who responded per onabotulinum toxin A treatment cycle are as follows: patients received a treatment every 3 months (155 U) for prophylaxis; among treated patients (N: 688) 49.3% had more than 50% reduction in headache day frequency during the first cycle (first 12 weeks). If there wasn't a response at the first cycle 11.3% responded at the second cycle and 10.3% responded at the 3rd cycle to obtain a 50% reduction in monthly migraine days [11]. Patients that had a lower number of monthly headache days at baseline in our study, such as in the Botox cohort with the add on of Erenumab and as in the no Botox cohort with an oral prophylaxis and add on of Erenumab, responded much better, possibly because of a lower level of central sensitization at baseline and fewer monthly migraine days [5-8]. Patients with medication overuse did not respond as well as patients without medication overuse. In this study we identified 4 hyper responders experiencing 2 migraine days per month.

The higher benefit in the Botox cohort and add on of Erenumab, may be related to the synergy of the action of Botulinum Toxin A which also blocks CGRP indirectly and of the action of the anti-CGRP monoclonal antibody [5].

Research findings identified Ad meningeal nociceptors as a likely site of action of Fremanezumab in the prevention of headache. The selectivity in its peripheral inhibitory action may partly account for a selective inhibition of high threshold as a result of a predominant Ad input to high threshold neurons, but not wide dynamic range dorsal horn neurons, and why it may not be effective in all migraine patients. Onabotulinum Toxin A can inhibit responses of C-Type meningeal nociceptors to stimulation of their intracranial dural receptive field by blocking TRPV1, TRPA1 ionic channels. Botulinum Toxin A produces no responsiveness of Ad fibers to mechanical and chemical stimulation [9,10].

Botulinum Toxin A has a local effect at the sites of injection on the head and neck, it improves neck pain and the presence of hyperalgesia, which is very frequent in chronic migraine patients [6]. In this study Erenumab did not improve neck pain and those patients that combined Botulinum Toxin A with Erenumab did not want to stop the Toxin because of the improvement of their neck pain.

As for the adverse events Botulinum Toxin A controls CGRP at the anatomical sites it is injected. Erenumab is administered sub-cutaneously and dispersed systemically. We Have identified 72 adverse events in patients receiving Erenumab. At baseline Botulinum Toxin A and the oral prophylactic drugs had been at a stable dose, and were well tolerated before entering this study.

Conclusion

Chronic migraineurs are very burdened with frequent monthly migraines, with frequent neck pain and hyperalgesia even more when patients have endured head and or neck trauma. Central sensitization is present [5-8].

There are no studies that have demonstrated the biological logic of combining two different drugs for the treatment of chronic

migraineurs, although it is a common practice. Our knowledge of the biology of pain in migraine has improved; Calcitonin Gene Related peptide (CGRP), Transient receptor vanilloid ionic channel (TRPV1), Prostaglandin E2 (PGE2), Nitric Oxide (NO) N Methyl D Aspartate (NMDA) and other substances are important in the process of migraine pain. The association of Botulinum Toxin A with Erenumab showed a significant reduction in the primary end point, mean change from baseline in monthly migraine days, the association of an oral prophylactic to Erenumab reduced the frequency of the patient's monthly migraine days although less than in the Botulinum Toxin A with Erenumab cohort. Erenumab alone was the least effective in reducing the frequency of the patient's monthly migraine days.

Botulinum Toxin A blocks de ligand CGRP in the sensory nerve endings [7]; Erenumab blocks the CGRP receptor. Botulinum Toxin A also reduces central sensitization and controls pain by other mechanism [7]. Could the synergy between Botulinum Toxin A and Erenumab with it's different effect on CGRP, explain the significant response in the Botox Erenumab cohort?

The prolonged duration of chronic migraine renders the treatment of these patients very difficult. The use of Botulinum Toxin A in chronic migraine is now standard care, efficacious, and paid by public and private payers in Quebec. Erenumab is efficacious in episodic migraine and chronic migraine but still has to be approved by public payers.

Acknowledgement

We thank our patients for there partnership in participating in this observational study. We thank our study coordinator Catherine Demers for her coordination in this study. We have not received any financial support for this study.

References

1. Stewart J. Tepper: Anti-Cacitonin Gene-Related peptide (CGRP) Therapies: Update on a Previous Review After the American Headache Society 60th Scientific Meeting. San Francisco, Headache. 2018; 58: 276-290.
2. David W Dodick. CGRP ligand and receptor monoclonal antibodies for migraine prevention: Evidence review and clinical implications. Cephalalgia. 2019; 39: 445-458.
3. Messoud Ashina, Stewart Tepper, Jan Lewis Brandes, et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double- blind, placebo-controlled study. Cephalalgia. 2018; 38: 1611-1621.
4. Marie Deen, Edvige Correnti, Katharina Kamm, et al. Blocking CGRP in migraine patients-a review of pros and cons. J Headache Pain. 2017; 18: 96.
5. Juntima Pleumsamran, Apisate Pleumsamran, Supang Maneesri-le Grand, et al. The role of calcitonin gene-related peptide in migraine prevention by Botulinum Toxin type A. Neurology Asia. 2018; 23: 45-53.
6. Paul L Durham, Roger Cady. Insights into the Mechanism of Onabotulinum toxin A in Chronic migraine. Headache. 2011; 51: 1573-1577.
7. Zdravko Lackovic, Boris Filipovic, Ivica Matak, et al. Activity of botulinum toxin type A in cranial dura implications for treatment of migraine and other headaches. Br J Pharmacol. 2016; 173: 279-291.
8. Guy P Boudreau: Clinical assessment of hyperalgesia and allodynia, in episodic migraine versus chronic migraine interictally and ictally. In Frontier in Headache Research Series; From basic pain mechanism to headache, edited by Jes Oleson and Troels Jensen, section IV.
9. Melo-Carrillo A, Strassman AM, Nir RR, et al. Fremanezumab-A humanized monoclonal anti CGRP antibody inhibits thin myelinated (Ad) but not unmyelinated (C) meningeal nociceptors. The Journal of neuroscience. 2017; 37: 10587-10596.
10. Zhang X, Strassman AM, Novack V, et al. Extracranial injections of botulinum toxin A inhibit intracranial meningeal nociceptors responses to stimulation of TRPV1 and TRPA1 channels. Cephalalgia. 2016; 36: 875-886.
11. Silberstein SD, Dodick DW, Aurora SK, et al. Per Cent of patients with chronic migraine who responded per onabotulinum A: PREEMPT. Journal Neurology Neurosurgery & Psychiatry. 2015; 86: 996-1001.