Spring 2023

A Comparison of Anti-Calcitonin Gene-Related Peptide Monoclonal Antibodies and Standard Migraine Prophylaxis in Those with Episodic Migraines

Alexie Harms
University of North Dakota

A Comparison of Anti-Calcitonin Gene-Related Peptide Monoclonal Antibodies and Standard Migraine Prophylaxis in Those with Episodic Migraines

Alexie Harms
Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences
Grand Forks, ND 58202-9037

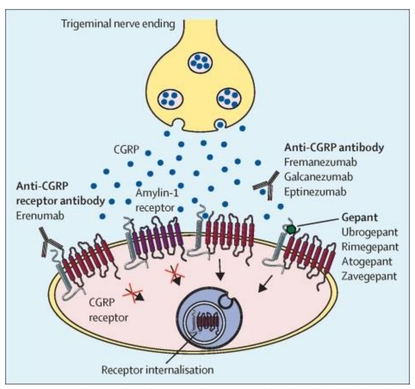
Abstract

Migraines are debilitating and a frequent reason for primary care visits. Migraines interfere with an individual's work, school, and daily life. Standard of care treatment options for migraine prophylaxis include Propranolol, Amitriptyline, and Topiramate which were all developed for other medical conditions. These conventional medications can lead to unwanted side effects decreasing treatment adherence. Calcitonin Gene-Related Peptide monoclonal antibodies (CGRP mAbs) have been under study for the treatment and prevention of migraines. The purpose of this research project is to explore the effectiveness and tolerability of CGRP mAbs in reducing the number of migraine days in comparison to conventional migraine prophylactic use for individuals who suffer from episodic migraines.

- Keywords: *migraine prevention, episodic migraines, CGRP mAbs, Propranolol, Amitriptyline, Topiramate, Eptinezumab, Galcanzumab, Fremanezumab, Erenumab*

Introduction

- CGRP: neuropeptide known to cause potent arterial vasodilation. Influences the trigeminovascular nociceptive system leading to sustained neurogenic inflammation and increased pain$_{12}$
- Studies have shown elevated levels of CGRP during migraine attacks. Inhibition of this neuropeptide has been under study for the treatment and prevention of migraine headaches.
- Four FDA approved CGRP mAbs that hinder the function of CGRP: Eptinezumab, Galcanzumab, Fremanezumab, Erenumab



Al-Hassany, L., Goadsby, P. J., Danser, J., & MaassenVanDenBrink, A. (2022). Calcitonin gene-related peptide-targeting drugs for migraine: How pharmacology might inform treatment decisions. *The Lancet, 21*(3), 284-294. DOI: 10.1016/S1474-4422(21)00409-9

Statement of the Problem

Current standard of care treatment options for migraine prophylaxis are poorly adhered to due to side effect profiles. Research is needed to show the efficacy, safety, and tolerability of other treatment options including CGRP mAbs for those suffering from migraines.

Research Questions

- ❖ In adults with episodic migraines with or without an aura, are CGRP mAbs more effective in reducing the frequency/number of migraine days than conventional migraine prophylactic use of Propranolol, Amitriptyline, or Topiramate?
- ❖ Is there a statistically or clinically significant difference in tolerability or adherence of CGRP mAbs as compared to conventional migraine prophylaxis?

Literature Review

Conventional Treatments

- While Topiramate and Propranolol are effective in reducing migraine days, drop out rates due to adverse reactions were 55% of those in the Topiramate 200mg, 28% in the Topiramate 100mg, and 10% in the Propranolol groups$_{2}$
- Topiramate and Amitriptyline are equally capable of reducing migraines, however 86% of those in the Topiramate group experienced adverse events with 20% discontinuing treatment and 89% in the Amitriptyline group had adverse events with 23% discontinuing$_{4}$

CGRP mAbs

- Eptinezumab at 300mg or 100mg decreases migraine days. About 60% of patients experienced an adverse reaction which included the placebo group but only six individuals dropped from the 100mg and five from the 300mg eptinezumab groups$_{1}$
  - Over one year those taking eptinezumab continued to have decreased migraine days and significant decreases in adverse reactions after the first dose$_{10}$
- Galcanezumab at 120mg and 240mg demonstrate a reduction in migraine days. Discontinuation due to adverse events was 2% from the 120mg, 4% from the 240mg, and 2% from the placebo$_{9}$
- Dodick et al. (2018) found fremanezumab decreased migraine days and discontinuation rates due to adverse reactions was 2% or less across all groups including the placebo$_{3}$
  - Study was expanded across one year and found continued reductions in migraines as well as 79% adherence to treatment$_{7}$
- Erenumab at 70mg and 140mg both decrease migraine days with 2% discontinuation rates due to adverse events in either group$_{5}$
  - Study was expanded across one year and found six in the 70mg group and ten in the 140mg group discontinued due to adverse reactions$_{6}$

Comparison

- A head-to-head trial conducted by Reuter et al. (2022) assessed the efficacy and tolerability of erenumab compared to Topiramate. 11% of patients in the erenumab group discontinued treatment due to adverse reactions compared to 39% in the Topiramate group. Erenumab also demonstrated greater reduction in migraine days (6 less days per month in the erenumab group compared to 4 less days in the Topiramate group)$_{8}$
- Varnado et al. (2022) found patients on a CGRP mAb (erenumab, fremanezumab, or galcanezumab) were less likely to discontinue their treatment over six and 12 month follow-up and were twice as likely to refill their medication as compared to those on a standard preventative treatment$_{11}$

Discussion

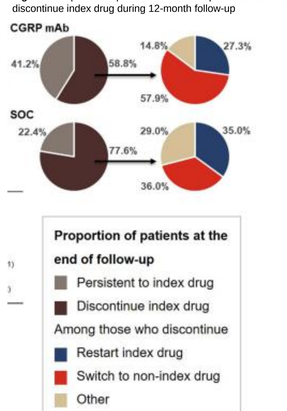
Effectiveness

- Topiramate, Amitriptyline, and Propranolol are all effective in reducing migraine frequency and decreasing the frequency in which individuals need to use abortive migraine medications$_{2;4}$
- No statistically significant difference in the effectiveness of Topiramate, Amitriptyline, or Propranolol in reducing migraine days, however Topiramate did demonstrate improvements in some quality-of-life areas and weight loss$_{2;4}$
- Eptinezumab, galcanezumab, fremanezumab, and erenumab, all were determined to be effective medications in the reduction of migraine days compared to a placebo$_{3;5;9;10}$
- Fremanezumab and erenumab demonstrated a decrease in activity impairment due to migraines$_{3;5}$
- Eptinezumab demonstrated improvements in bodily pain and social functioning$_{10}$
- Erenumab and eptinezumab groups demonstrated improvements in physical health$_{5;10}$
- Galcanezumab was found to decrease the overall severity of the migraine itself$_{9}$
- Only one head-to-head study comparing the two groups of medications. It was determined in this study that CGRP mAbs demonstrated superiority over standard treatment in decreasing migraine days. Erenumab also demonstrated a significantly greater decrease in the impact of migraines on social and cognitive functioning, psychological and physical health, and energy level following treatment compared to Topiramate$_{8}$

Tolerability

- Topiramate, Amitriptyline, and Propranolol demonstrated similar side effect profiles including paresthesia, difficulty concentrating, nausea, fatigue, insomnia, anorexia, dry mouth, somnolence, and dizziness with large discontinuation rates$_{2;4}$
- Those taking Propranolol and Amitriptyline experienced clinically significant increase in weight$_{2;4}$
- Injection site pain and reaction were the most common adverse events for those receiving a CGRP mAb$_{3;9}$
- Discontinuation rates among CGRP mAb and placebo groups were similar across several studies$_{1;3;5;9}$
- Over 81% of those receiving Topiramate demonstrated adverse reactions with 39% discontinuing treatment compared to 55% in the erenumab group with 11% discontinuing$_{8}$
- Treatment adherence is higher for those receiving a CGRP mAb over any of the standard of care prophylactic treatments with discontinuation rates for standard of care nearly 80% whereas those in the CGRP mAb group was about 59%$_{11}$
- 50% of patients discontinued their conventional migraine prophylactic treatment within one month of initiation, while less than 20% discontinued their CGRP mAb$_{11}$

Figure 3 Proportion of patients that remain persistent to and discontinue index drug during 12-month follow-up



Varnado, O. J., Manjelievskaia, J., Ye, W., Perry, A., Schuh, K., & Wenzel, R. (2022). Treatment patterns for calcitonin gene-related peptide monoclonal antibodies including galcanezumab versus conventional preventive treatments for migraine: A retrospective US claims study. *Patient Preference and Adherence, 16*, 821-839. DOI: 10.2147/ppa.s346660

Applicability to Clinical Practice

- ➢ Migraines have a significant impact on the quality of life for patients who suffer from them.
- ➢ Current standard of care migraine prophylaxis medications come with unwanted side effects leading to decreased compliance.
- ➢ Tolerability and adherence are needed for successful migraine prevention.
- ➢ CGRP mAbs may be a viable treatment option with increased tolerability, safety, and efficacy.

Acknowledgements

I would like to thank my scholarly project and PA program advisor Russell Kauffman for his guidance and support throughout this project and program. I would also like to express my gratitude to Dr. Anne Haskins for her time and assistance regarding statistics, Megan Denis, MLIS at UND's Library Resources for her supervision and support with research, and Dr. Benjamin Krogh for his preceptorship, expertise, and insight on clinical application of my project. Lastly, I would like to thank my husband Gunther, family, friends, and my UND PA colleagues for all their support throughout PA school.

References

1. Ashina, M., Saper, J., Cady, R., Schaeffler, B., Biondi, D., Hirman, J., Pederson, S., Allan, B., & Smith, J. (2020). Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-I). *Cephalalgia, 40*(3), 241-254. DOI: 10.1177/0333102420905132
2. Diener, H., Tfelt-Hansen, P., Dahlof, C., Lainez, M., Sandrini, G., Wang, S., Neto, W., Vijapurkar, U., Doyle, A., & Jacobs, D. (2004). Topiramate in migraine prophylaxis: Results from a placebo-controlled trial with propranolol as an active control. *Journal of Neurology*, *251*(8), 943–950. DOI: 10.1007/s00415-004-0464-6
3. Dodick. D. W., Ashina, M., Brandes, J. L., Kudrow, D., Lanteri-Minet, M., Osipova, V., Palmer, K., Picard, H., Mikol, D. D., & Lenz, R. A. (2018). ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia, 38*(6), 1026-1037. DOI: 10.1177/0333102418759786
4. Dodick, D. W., Freitag, F., Banks, J., Saper, J., Xiang, J., Rupnow, M., Biondi, D., Greenberg, S. J., & Hulihan, J. (2009). Topiramate versus amitriptyline in migraine prevention: A 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. *Clinical Therapeutics*, *31*(3), 542–559. DOI: 10.1016/j.clinthera.2009.03.020
5. Goadsby, P. J., Reuter, U., Hallstrom, Y., Broessner, G., Bonner, J. H., Zhang, F., Sapra, S., Picard, H., Mikol, D. D., & Lenz, R. A. (2017). A controlled trial of erenumab for episodic migraine. *The New England Journal of Medicine, 377*(22), 2123-2132. DOI: 10.1056/NEJMoa1705848
6. Goadsby, P. J., Reuter, U., Hallstrom, Y., Broessner, G., Bonner, J. H., Zhang, F., Wright, I. K., Chou, D. E., Klatt, J., Picard, H., Lenz, R. A., & Mikol, D. D. (2020). One-year sustained efficacy of erenumab in episodic migraine: Results of the STRIVE study. *Neurology, 95*(5), 469-479. DOI: 10.1212/WNL.0000000000010019
7. Goadsby, P. J., Silberstein, S. D., Yeung, P. P., Cohen, J. M., Ning, X., Yang, R., & Dodick, D. W. (2020). Long-term safety, tolerability, and efficacy of fremanezumab in migraine. *Neurology, 95*(18), 2487-2499. DOI: 10.1212/WNL.0000000000010600
8. Reuter, U., Ehrlich, M., Gendolla, A., Heinze, A., Klatt, J., Wen, S., Hours-Zesiger, P., Nickisch, J., Sieder, C., Hentschke, C., & Maier-Peuschel, M. (2022). Erenumab versus topiramate for the prevention of migraine – a randomised, double-blind, active-controlled phase 4 trial. *Cephalalgia, 42*(2), 108-118. DOI: 10.1177/03331024211053571
9. Skljarevski, V., Matharu, M., Millen, B. A., Ossipov, M. H., Kim, B., & Yang, J. Y. (2018). Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia, 38*(8), 1442-1454. DOI: 10.1177/0333102418779543
10. Smith, T. R., Janelidze, M., Chakhava, G., Cady, R., Hirman, J., Allan, B., Pederson, S., Smith, J., & Schaeffler, B. (2020). Eptinezumab for the prevention of episodic migraine: Sustained effect through 1 year of treatment in the PROMISE-1 study. *Clinical Therapeutics, 42*(12), 2254-2265. https://doi.org/10.1016/j.clinthera.2020.11.007
11. Varnado, O. J., Manjelievskaia, J., Ye, W., Perry, A., Schuh, K., & Wenzel, R. (2022). Treatment patterns for calcitonin gene-related peptide monoclonal antibodies including galcanezumab versus conventional preventive treatments for migraine: A retrospective US claims study. *Patient Preference and Adherence, 16*, 821-839. DOI: 10.2147/ppa.s346660
12. Yuan, H., Lauritsen, C. G., Kaiser, E. A., & Silberstein, S. D. (2017). CGRP monoclonal antibodies for migraine: Rationale and progress. *BioDrugs, 31*(6), 487-501. DOI: 10.1007/s40259-017-0250-5