Dual Calcitonin Gene-Related Peptide Antagonists for Chronic Migraine Prevention

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Background

- Chronic migraine affects approximately 1-2 percent of the global population.[1]
- Calcitonin gene-related peptide (CGRP) is a vasodilator and neuropeptide that plays a role in migraine pathophysiology.[2]
- CGRP antagonists were specifically developed for migraine prophylaxis. All other medications used for migraine prevention were developed for other reasons, with migraine benefits discovered at a later time.[3]
- The combination of acute and preventive CGRP antagonists have been reported to be potentially safe and efficacious.[2]
- There is limited literature discussing the potential of using two concurrent preventive CGRP agents.[2]

Objective

Evaluate the safety and efficacy of two concurrent preventive CGRP agents for the treatment of chronic migraine.

Methods

An IRB-approved retrospective review of patients treated at the University of Vermont Health Network. Each patient served as their own control, with data collected at two points: just before starting the second preventive CGRP agent and after a minimum of 3 to 6 months on two preventive CGRP antagonist agents. Analysis on outcome data was done using a Wilcoxon signed-rank test.

Inclusion Criteria:

- Adult patients with chronic migraine
- Concurrent use of one preventive CGRP from each of the following categories:
  - **mAbs:** erenumab (Aimovig®), fremanezumab (Ajovy®), galcanezumab (Emgality®), or eptinezumab (Vyepti®)
  - **gepants:** rimegepant (Nurtec®) or atogepant (Qulipta®)

Exclusion Criteria:

- Patients on two mAbs or two preventive gepants
- Patients on one preventive CGRP antagonist for less than 3 months before addition of second preventive CGRP
- Patients who have only taken rimegepant (Nurtec®) as abortive rather than preventive dosing in combination with an injectable CGRP without using a separate preventive gepant

Outcomes:

Primary:

- Compare number of headache days per month while on one preventive CGRP to the number of headache days per month after starting a second preventive CGRP therapy.

Secondary:

- Compare side effects, number of migraine or severe headache days, and abortive medication use between one and two preventive CGRPs.
- Review reasons for discontinuation of dual therapy

Demographics

Characteristic (n=37)	N (%)
Mean Age (years)	54
Female Gender	32 (86.4)
White Race	35 (94.6)
Not Hispanic or Latino	37 (100)
Insurance	
Medicare	8 (21.6)
Medicaid	6 (16.2)
Commercial	21 (56.8)
Non-CGRP Migraine Prevention	
Beta Blockers	20 (54.1)
Botulinum Toxin	27 (73.0)
Candesartan	14 (37.8)
Divalproex Sodium	17 (45.9)
Lisinopril	8 (21.6)
Memantine	8 (21.6)
SNRIs	21 (56.8)
Topiramate	31 (83.8)
TCAs	28 (75.7)
Verapamil	7 (18.9)
Mean non-CGRP trialed agents	5.5

Comorbidities	
Anxiety	29 (78.4)
Depression	25 (67.6)
Hypertension	13 (35.1)
Seizure	2 (5.4)

Migraine Duration (years)	N (%)
< 5 years	2 (5.4)
5 to 9	8 (21.6)
10 to 14	12 (32.4)
15 to 19	7 (18.9)
20 or more	8 (21.6)

First CGRP	
Galcanezumab	11 (29.7)
Eptinezumab	4 (10.8)
Fremanezumab	8 (21.6)
Erenumab	6 (16.2)
Atogepant	5 (13.5)
Rimegepant	3 (8.1)
Second CGRP	
Atogepant	14 (37.8)
Rimegepant	15 (40.5)
Eptinezumab	4 (10.8)
Galcanezumab	4 (10.8)

CGRP Timing	
Average Time to Second CGRP Start (years)	1.52 (0.32 - 4.94)

Results

Primary Outcome	
Change in Headache Frequency (n=37)	
Mean Change (days)	-2.92 (p=0.0329)
Interquartile Range	5 (-5, 0)
Proportion with ≥ 50% Reduction in Headache Days	20.4%
Secondary Outcome	
Change in Migraine/Severe Headache Days (n=35)	
Mean Change (days)	-3.14 (p=0.0014)
Interquartile Range	6 (-6, 0)
Change in Days of Rescue Medications Taken in a Month (n=4)	
Mean Change (days)	-2.75

Dual Therapy Discontinuation (n=37)	
Discontinuation Frequency	19 (51.4)
Reasons for Discontinuation	
Adverse Event	0 (0)
Insurance Coverage	7 (18.9)
Lack Perceived Benefit	12 (32.4)

Adverse effect was reported by 7 (9.5%) patients. One patient reported two adverse effects, and the other six patients had one. The reported adverse effects included nausea, fatigue, injection site reaction, and injection site pain. None of the adverse effects lead to treatment discontinuation.

Discussion

- Dual CGRP antagonist preventives may be a viable and well-tolerated option for migraine prevention in patients with chronic migraine who are treatment resistant.
- If dual preventive CGRP antagonist therapy was discontinued, it was due to insurance coverage changes or lack of perceived benefit rather than adverse effects.
- One preventive CGRP antagonist alone may not provide the full potential efficacy from blocking the CGRP migraine pathway.
- Gepants block the CGRP receptor while -mAbs block the CGRP ligand (exception is erenumab which blocks the receptor), a possible mechanism for a synergistic effect.
- Further studies are needed to confirm safety, efficacy, and mechanism of synergism.

Limitation

- Included patient sample is small and study used secondary data.
- Migraine assessments relies on accurate patient reporting.
- There is variability in documentation by different providers.
- Change in acute medication use was recorded as a discrete number for just 4 of 37 patients

Conclusion

Dual CGRP antagonist preventives may be a viable and well-tolerated option for migraine prevention in patients with chronic migraine who are treatment resistant.

References

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