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Role of Monoclonal Antibodies against Calcitonin Gene-Related Peptide (CGRP) in Episodic Migraine Prevention: Where Do We Stand Today?

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Abstract:

Background: Medications targeting the calcitonin gene-related peptide (CGRP) pathway are exciting and novel therapeutic options in the treatment of migraine.

Objective: In this article, we have reviewed the role of these CGRP monoclonal antibodies in patients with episodic migraine.

Materials and Methods: We did an extensive literature search for all phase 2 and 3 studies involving CGRP monoclonal antibodies in episodic migraine.

Results: Erenumab, fremanezumab, galcanezumab, and eptinezumab have all undergone phase 3 trials and have been found to be effective for episodic and chronic migraine. They have the advantage of being targeted therapies for migraine with very favorable adverse effect profiles comparable to placebo. Importantly, they are effective in subgroups of patients who have failed previous preventive therapies.

Conclusion: Increasing use of these medications will certainly revolutionize the treatment and outlook for patients with migraine all over the world.

Key Words:

Calcitonin gene-related peptide (CGRP), episodic migraine, eptinezumab, erenumab, fremanezumab, galcanezumab, monoclonal antibodies

Key Messages:

CGRP monoclonal antibodies are revolutionizing the therapeutic armamentarium of physicians involved in the management of migraine. They are the first group of medications to be specifically designed for the prophylaxis of migraine. They have already become the standard of care in chronic migraine. Considering their efficacy and favorable side effect profile, they will increasingly be used in the setting of episodic migraine as well.

Migraine is a common neurological disorder characterized by recurrent attacks of moderate to severe headache with accompanying symptoms such as nausea, photophobia or phonophobia.[1] Attacks typically last between 4 and 72 h and may be preceded by aura in up to one-third of patients. Based on the criteria in the International Classification for Headache Disorders- Third Edition (ICHD-3),[2] migraine is often subclassified as migraine without aura, migraine with aura, or chronic migraine (≥15 headache days per month of which ≥8 are migraine headaches for more than 3 months). Episodic migraine is characterized by those with migraine who have 0 to 14 headache days per month.[3]

Episodic migraine continues to be inadequately treated as shown by the fact that only around 20% of patients receive a migraine-specific treatment.[4] This raises concern as ineffective acute treatment is associated with a twofold increased risk of new-onset chronic migraine.[5] Moreover, in the USA only one-third of patients where preventives are indicated receive them.[6]

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Preventive medication for migraine, such as anti-epileptics (e.g., valproic acid, topiramate), antidepressants (e.g., amitriptyline), antihypertensives (e.g. propranolol, candesartan), and miscellaneous other drugs have shown efficacy in reducing the number of migraine days in episodic migraine. However, many of these drugs have limitations in clinical practice due to problems with tolerability, safety, or adherence. Compliance to oral preventive medications is low and the percentages of patients adhering to treatment drop over time.[7]

Newer medications targeting the calcitonin gene-related peptide (CGRP) pathway constitute the single biggest advance made in the treatment of migraine in the last few decades. Unlike the previous medications used as preventives for migraine, the new medications are migraine-specific and have an improved side effect profile.

As we write, out of four CGRP pathway monoclonal antibodies, erenumab, fremanezumab, and galcanezumab have been approved by regulators for the prevention of episodic and chronic migraine. Eptinezumab has been approved by the FDA but is undergoing evaluation by the EMA.

Structure and Function of the CGRP Monoclonal Antibodies

CGRP is a 37 amino-acid neuropeptide that is abundantly present in trigeminal sensory nerve fiberss and the central nervous system.[8] The molecule CGRP in its alpha isoform is strongly present in the C-fibres of the trigeminal nerve and plays an important role in the trigeminovascular system. CGRP, in addition to the CLR – RAMP 1 receptor also binds to adrenomedullin –1 and 2, calcitonin and amylin receptors.[9]

CGRP is released during migraine attacks in the extracerebral circulation.[10] Furthermore, during electrical stimulation of the trigeminal ganglion, CGRP levels in the jugular vein increased and were reversed after administration of sumatriptan and dihydroergotamine.[11] Intravenous administration of CGRP has the potential to evoke migraine attacks in migraine patients but not in controls.[12,13]

Four monoclonal antibodies have now been developed to target the CGRP pathway. Before the development of monoclonal antibodies, small molecules targeting the CGRP receptor were developed but were initially withdrawn from further development due to drug-induced hepatotoxicity.[14] Erenumab binds to and blocks the canonical CGRP receptor: CLR – RAMP 1 complex,[15] whereas the other three molecules bind to the CGRP ligand itself. The dosing frequency is monthly for erenumab and galcanezumab, monthly or quarterly for fremanezumab, and quarterly for eptinezumab. Galcanezumab has high binding affinity to human CGRP and fremanezumab has the longest half-life (t1/2) as measured, suggesting longer dosing intervals, although what is appropriate to measure for the migraine effect is unsettled.[16,17] Erenumab, fremanezumab, and galcanezumab are available as subcutaneous injections, while eptinezumab is only available as an I.V. formulation. Their long half-lives bring the advantage of less frequent dosing as compared to oral preparations. A summary of the different characteristics of the four monoclonal antibodies can be found in Table 1.

Efficacy of CGRP Monoclonal Antibodies in Episodic Migraine

Erenumab

Erenumab as shown in Table 4 has completed one phase 2 study,[18] two phase 3 studies (STRIVE and ARISE)[19,20] and one phase 3b study (LIBERTY).[21] All the studies included patients of episodic migraine who had failed 2 or less preventives except LIBERTY, which enrolled patients with prior failure of 2–4 preventives. All the trials used 70 mg dose except LIBERTY which used the 140 mg dose. STRIVE had both 70 mg and 140 mg arms.

The phase 3 ARISE study investigated episodic migraine patients with 4 to 14 days of headache per month. At week 12, the erenumab 70 mg group had a significant reduction of mean monthly migraine days (MMD's) compared to the placebo group. A significant reduction in monthly migraine-specific medication days (MSMD's) and disability scores such as MIDAS were also noted. The 50% responder rate was 39.7% in the active treatment group compared to 29.5% in the placebo group.

In phase 3 STRIVE study, patients between 18 and 65 years old were randomized to erenumab 70 mg, erenumab 140 mg monthly or placebo. At 12 weeks, the reduction in MMD was –3.2 in the erenumab 70 mg group, - 3.7 in the 140 mg group, and –1.8 days in the placebo group ($P < 0.001$ both groups versus placebo). The 50% responder rate was significantly higher in the 140 mg group (50%) and the 70 mg group (43.3%) compared to the placebo group 26.6%. There

Table 1: Summary of pharmacodynamic and pharmacokinetic properties of the four anti-CGRP pathway monoclonal antibodies

Name	IgG type	Administration	Target	Half-life	Cmax
Erenumab (AMG334)	IgG2 human	SC injections; 70 mg or 140 mg every 4 weeks	CGRP canonical receptor (CLR/RAMP1)	28 days	6 days
Eptinezumab (ALD403)	IgG1 humanized	IV infusion; 30 mg, 100 mg or 300 mg quarterly	Alpha-CGRP, beta-CGRP	27 days	3 h
Galcanezumab (LY2951742)	IgG4 humanized	SC injections; 240 mg loading dose, 120 mg monthly afterwards	Alpha-CGRP, beta-CGRP	27 days	5 days
Fremanezumab (TEV-48125)	IgG2 humanized	SC injections; 675 mg quarterly or 225 mg monthly	Alpha-CGRP, beta-CGRP	30 days	5-7 days

CLR = calcitonin receptor-like; CGRP = calcitonin gene-related peptide; Cmax = maximum serum concentration; IgG = immunoglobulin G; IV = intravenous; RAMP1 = receptor activity modifying protein 1; SC = subcutaneous.

Table 2: Study characteristics and results of fremanezumab

Study phase	Study design	No. of patients	Treatment arms	Treatment duration	Mean change in migraine days	*P*	50% responder rate	*P*	Mean change in monthly acute treatment days	*P*
IIb NCT02025556[16]	Randomised placebo controlled trial	104	placebo	12 weeks	-3.46		28%		-3.1	
		95	225 mg		-6.27	<0.0001	53%	0.005	-4.86	0.0018
		96	675 mg		-6.09	<0.0001	59%	<0.001	-4.8	0.0026
III HALO-EM NCT02629861[17]	Randomised placebo controlled trial	294	placebo	12 weeks	-2.2		27.9%		-1.6	
		290	225 mg		-3.7	<0.001	47.7%	<0.001	-3.0	<0.001
		294	675 mgfollowed by monthly placebo		-3.4	<0.001	44.4%	<0.001	-2.9	<0.001
III b FOCUS[26]	Randomised placebo controlled trial	112	Placebo	12 weeks	-0.7					
		110	Monthly 225 mg		-3.8	<0.0001				
		107	Quarterly 675 mg		-3.7	<0.0001				

Table 3: Study characteristics and results of galcanezumab

Study phase	Study design	No. of patients	Treatment arms	Treatment duration	Mean change in migrainoe days	*P*	50% responder rate	*P*	Mean change in monthly migraine specific treatment days	*P*
II NCT01625988[33]	Randomised placebo-controlled trial	110	Placebo	12 weeks	-3.0	0.003	45%			
		107	150 mg		-4.2		70%			
IIb NCT02163993[34]	Randomised, placebo-controlled trial	383	Placebo	3 months	-3.4		61.9%			
		68	5 mg		-4.3	0.02	75.8%	0.03		
		68	50 mg		-4.3	0.02				
		70	120 mg							
		67	300 mg							
III EVOLVE-1 NCT02614183[35]	Randomised, placebo-controlled trial	433	Placebo	6 months	-2.8		38.6%		-2.2	
		213	120 mg		-4.7	<0.001	62.3%	<0.001	-4.0	<0.001
		212	240 mg		-4.6	<0.001	60.9%	<0.001	-3.8	<0.001
III EVOLVE-2 NCT02614196[36]	Randomised, placebo-controlled trial	461	Placebo	6 months	-2.3		36%		-1.9	
		231	120 mg		-4.3	<0.001	59.3%	<0.001	-3.7	<0.001
		223	240 mg		-4.2	<0.001	56.5%	<0.001	-3.6	<0.001

Table 4: Study characteristics and results of erenumab

Study phase	Study design	No. of patients	Treatment arms	Treatment duration	Mean change in migraine days	*P*	50% responder rate	*P*	Mean change in monthly migraine specific treatment days	*P*
II NCT01952574[18]	Randomised, placebo-controlled trial	160	placebo	12 weeks	-2.3		30%		-0.7	
		108	7 mg		-2.2	0.82	29%	0.8	-0.6	0.71
		108	21 mg		-2.4	0.83	34%	0.44	-0.6	0.8
		107	70 mg		-3.4	0.021	46%	0.011	-1.6	0.004
II NCT01952574	Open-label extension	383	70 mg increased to 140 mg	256 weeks						
III STRIVE NCT02456740[19]	Randomised, placebo-controlled trial	319	Placebo	12 weeks followed by 28 weeks open label	-1.8		26.6%		-0.2	
		317	70 mg		-3.2	<0.001	43.3%	<0.001	-1.1	<0.001
		319	140 mg		-3.7	<0.001	50%	<0.001	-1.6	<0.001
III ARISE NCT02483585[20]	Randomised, placebo-controlled trial	291	Placebo	12 weeks followed by 28 weeks open label	-1.8		29.5%		-0.6	
		286	70 mg		-2.9	<0.001	39.7%	0.01	-1.2	0.002
IIIb LIBERTY NCT03096834[21]	Randomised, placebo-controlled trial	121	Placebo	12 weeks followed by 156 weeks open label	-0.2		14%		0.5	
		125	140 mg		-1.8	0.004	30%	0.002	-1.3	<0.001

was a reduction in the monthly migraine-specific medication days (MSMD) by –1.6 days in the 140 mg group, -1.1 days in the 70 mg group as compared to – 0.2 days in the placebo group ($P < 0.001$ both groups versus placebo).

There was a reduction of MMD's as compared to baseline with the 70 and 140 mg dose of -4.2 days and –4.9 days, respectively, in the extension of the STRIVE study. The 50% responder rates were 61% and 64.9%, respectively.[22]

Table 5: Study Characteristics and results of Eptinezumab

Study phase	Study design	No. Of patients	Treatment arms	Treatment duration	Mean change in migraine days	*P*	50% migraine responder rate	*P*	Mean change in monthly migraine specific treatment days	*P*
III PROMISE-1[40]	Randomised, placebo-controlled trial	222	Placebo q12w	56 weeks	-3.2		37.4%			
		221	100 mg IV q12w		-3.9	0.018	49.8%	0.0085		
		222	300 mg IV q12w		-4.3	<0.001	56.3%	0.0001		

Erenumab was effective even in the subgroups who had failed previous preventives. Data from the open-label phase of the LIBERTY study demonstrated changes from baseline of −2.7 MMD and − 1.4 MSMDs.[23] Overall, 39.2% of patients achieved a 50% reduction.[23] Subgroup analyses of the patient population of the STRIVE study which had tried and failed prior migraine preventives were also carried out. In the group of patients who have failed at least one preventive, there was a change in MMD of −2.0 days ($P < 0.001$) and −2.5 ($P < 0.001$) with erenumab 70 and 140 mg, respectively, at 6 months from baseline.[24] There was a significant reduction in MMD's even at the end of 1 year.[25] A similar result was observed in patients who failed two or more preventives, with a change of −1.3 ($P = 0.05$) and −2.7 ($P < 0.001$) with erenumab 70 and 140 mg, respectively, at 6 months from baseline.[24] The change in MSMDs in the group of patients who had previously failed at least one preventive was −1.5 ($P < 0.001$) and −2.1 ($P < 0.001$) in the 70 and 140 mg treatment groups, respectively, at 6 months from baseline.[24] A significant reduction of MSMD's was seen in the 1-year data as well.[25] Similarly, in patients who failed two or more preventives, the change observed was −1.2 ($P < 0.001$) and −2.5 ($P < 0.001$).[24] The 50% responder rate was lower in patients who had previously failed a preventive compared with treatment-naive patients. However, it was still significantly greater than the response seen in the placebo group. In the group who had previously failed one or more preventives, the proportion was 38.6% ($P < 0.001$) and 39.7% ($P < 0.001$) for doses of 70 and 140 mg, compared with 17.5% in the placebo group at 6 months.[24] Similarly, in the group who failed two or more preventives, the proportion was 26.5% ($P < 0.001$) and 36.2% ($P < 0.001$) for doses of 70 and 140 mg, compared with 11.1% in the placebo group.[25]

Fremanezumab

This molecule was evaluated as shown in Table 2 by one phase 2b study[16] and two phase-3 studies (HALO – EM)[17] and FOCUS.[26]

The phase 2b study included patients of episodic migraine between 18-65 years of age in which 225 mg and 675 mg subcutaneously monthly were compared with placebo. At 12 weeks, there was a reduction in MMD of −6.27 in the 225 mg group, -6.09 in the 675 mg group and −3.46 in the placebo group ($P < 0.0001$ both groups versus placebo). The 50% responder rate was significantly greater in the 225 mg group (53%) and 675 mg group (59%) as compared to the placebo group (28%). There was a significant decrease in the monthly acute treatment days in the fremanezumab treatment groups as compared to the placebo groups.

The HALO −EM study included patients with episodic migraine between 18-70 years of age and onset before the age of 50 years. In this study, two treatment arms (225 mg monthly subcutaneously and 675 mg subcutaneously once followed by 2 months of placebo) were compared to a placebo arm. At 12 weeks, there was a reduction in MMD of −3.7 in the 225 mg group, −3.4 in the 675 mg group, and −2.2 in the placebo group ($P < 0.001$ both groups versus placebo). The 50% responder rate was significantly greater in the 225 mg group (47.7%) and 675 mg group (44.4%) as compared to the placebo group (27.9%). There was a reduction in the monthly acute treatment days in the treatment groups (-3.0 days in the 225 mg group and −2.9 days in the 675 mg group) as compared to −1.6 days in the placebo group ($P < 0.001$ both groups versus placebo).

In an extension study that included patients from HALO – EM as well as new patients,[27] reduction of MMD's and MSMD's were significant as compared to baseline. The 50% responder rates on fremanezumab were 68% and 66% respectively.[28,29]

The FOCUS study[26] included both episodic and chronic migraine patients aged 18 −70 years with documented failure of 2-4 preventives. At 12 weeks, the reduction in MMD's was −3.8 and −3.7 in the monthly and quarterly fremanezumab group respectively as compared to −0.7 in the placebo group ($P < 0.0001$ both groups vs placebo). This was seen in the episodic migraine subgroup.

For patients in the HALO-EM study who had previously failed at least one preventive and were treated with either 225 mg monthly or 675 mg quarterly, there was a change in MMD of −3.7 ($P = 0.0015$) and − 3.3 ($P < 0.001$), respectively, compared with −1.3 in the placebo arm.[30] The 50% responder rates were 42% ($P = 0.0015$), 38% ($P = 0.0015$) and 18%, respectively. The change in MSMDs was −3.4 ($P < 0.001$), −3.1 ($P < 0.001$) and −1.1, respectively.[31]

Fremanezumab has also been found effective in high-frequency episodic migraine (16) and has led to a reduction in associated symptoms of migraine and migraine-specific medications.[32]

Galcanezumab

Galcanezumab was evaluated in two phase-2 trials[33,34] and two phase 3 trials, EVOLVE −1 and EVOLVE – 2[35,36] in which 120 mg and 240 mg were assessed as shown in Table 3. There was a significant reduction in MMD's in the galcanezumab arms as compared to placebo in all the trials. In EVOLVE-1, galcanezumab significantly reduced mean monthly headache days by 4.7 days (120 mg) and 4.6 days (240 mg) in comparison to placebo (2.8 days). In EVOLVE-2, Mean monthly migraine headache days decreased by 4.3 in the galcanezumab 120 mg monthly group and 4.2 days in the 240 mg monthly group, compared to 2.3 days in the placebo group. The 50% responder rates were higher in the galcanezumab groups. In EVOLVE-1, 60.9% in the 240 mg monthly group and 62.3% of patients in the 120 mg monthly group reached ≥ 50% response compared

to 38.6% in the placebo group. In EVOLVE-2, 57% in the 240 mg monthly group and 59% of patients in the 120 mg monthly group reached ≥50% response compared to 36% in the placebo group. There was a significant reduction in the MSMD's in the galcanezumab arms as compared to placebo in all the trials. In EVOLVE –1, there was a reduction of MSMD by –4.0 in the 120 mg group, -3.8 in the 240 mg group, and –2.2 in the placebo group ($P < 0.001$ both groups versus placebo). In EVOLVE –2, there was a reduction in MSMD by –3.7 in the 120 mg group, -3.6 in the 240 mg group, and –1.9 in the placebo group ($P < 0.001$ both groups versus placebo). The onset of efficacy is usually within 1 week of starting treatment and early nonresponders are likely to achieve a response by month 2 or 3.[37]

Subgroup analysis of patients from the EVOLVE 1 and EVOLVE 2 studies who had previously tried and failed two or more preventives, showed a reduction in MMD with galcanezumab 120 mg of –3.45 days ($P < 0.001$) and – 3.85 days ($P < 0.001$), compared with – 0.81 in the placebo group.[38] In this analysis, a significantly greater percentage of patients in the galcanezumab 120 and 240 mg treatment groups also achieved a 50% response compared with the placebo group.[38] Subgroup analyses showed that galcanezumab significantly reduced migraine headache days (MHD's) in both the low frequency and high-frequency episodic migraine groups with a reduction in the associated symptoms of migraine.[39]

Eptinezumab

The PROMISE –1 phase 3 trial evaluated eptinezumab in the doses of 30, 100, and 300 mg against placebo as shown in Table 5.[40] Patients aged 18 – 75 years with episodic migraine (4-14 headache days out of which there are at least 4 migraine days) were recruited for the study. Those with medication overuse headache were excluded. A significant reduction in MMD's at week 12 as compared to baseline was seen in all the treatment groups, which persisted at the end of 10-12 months as seen in the 1-year data.[40] The 50% responder rates were significantly higher in the treatment arms (49.8% in the 100 mg group and 56.3% in the 300 mg group) as compared to 37.4% in the placebo group. There was a further improvement at the end of 10-12 months.[40]

Eptinezumab is seen to have a rapid effect on migraine within day 1 after infusion. In the PROMISE –1 study, migraine rates on day 1 were 14.8% in the 100 mg group, 13.9% in the 300 mg group and 22.5% in the placebo group.[40] The same phenomenon was seen in the phase 2 study.[41] This may be due to the intravenous route of administration and consequent high Tmax.

Safety Data and Adverse Effects

Overall safety data for all 4 compounds have been generally good. Studies have reported very few serious adverse events and most were deemed not to be caused by the monoclonal antibodies. The adverse event rates were found to be similar in the treatment and placebo arms of the ARISE,[20] STRIVE[19] and HALO – EM[17] studies.

A meta-analysis of erenumab phase 2 and 3 trials reveals no significant difference in adverse events, serious adverse events and discontinuation due to adverse events.[42]

A meta-analysis of adverse events from phase 2 and 3 studies of episodic migraine have shown significant differences in the rate of adverse events between fremanezumab treatment and placebo arms. However, no specific adverse event was significantly different between the 2 arms.[43,44]

As regards galcanezumab, in the EVOLVE – 1 study,[35] injection site reaction and pruritus were significantly more common in the treatment group ($P < 0.05$). In the EVOLVE –2 study,[36] injection site reactions were significantly more common in the 120 mg and 240 mg treatment arms as compared to the placebo arm ($P < 0.001$). Adverse effects were also dose-dependent, with a higher frequency seen in the 240 mg treatment arm.

A meta-analysis of adverse events in phase 2 and 3 galcanezumab trials have shown a significantly higher chance of injection site reactions.[43,44]

In the PROMISE –1 study, there was no apparent dose-related trend in the nature, frequency, and severity of treatment-emergent adverse events (TEAE).[40]

The most commonly reported adverse events for each drug have been documented in Table 6.

The most common side effect of the monoclonal antibodies is injection site reaction, which is usually mild and self-limiting.

CGRP is a potent vasodilator[45] and has an antihypertensive action in experimental settings.[46] There have been concerns that inhibition of CGRP mediated vasodilatation through CLR/RAMP 1 receptors located in the smooth muscle cells lining the coronary and cerebral vasculature may increase the risk of myocardial infarction and other vascular events. However, *in vitro* experiments have shown that even though erenumab antagonizes CGRP induced vasorelaxation, vasorelaxation by alternative pathways (nicardipine and substance P) remains intact. This suggests that vasodilatation is possible in the presence of CLR/RAMP 1 antagonism.[47] In phase 2 and 3 trials of these CGRP monoclonal antibodies, there were no reports of changes in blood pressure, heart rate, or the electrocardiogram. A recent analysis of data from phase III chronic and episodic migraine trials with galcanezumab,[48] phase IIb and III chronic and episodic migraine trials with fremanezumab,[49] and meta-analysis of phase II and III chronic and episodic migraine trials of erenumab[42] have shown no increased risk of cardiac or cerebral adverse outcomes. However, a retrospective study of post marketing safety data

Table 6: Most common adverse events (as mentioned in the summary of product characteristics)

Name	Common adverse events
Erenumab	Hypersensitivity reactions (including anaphylaxis, angioedema, rash, swelling/oedema and urticaria), injection site reactions, constipation, muscle spasms, pruritus
Eptinezumab	Nasopharyngitis, hypersensitivity reactions
Galcanezumab	Injection site pain, reaction and erythema, constipation, vertigo, pruritus, rash, urticaria
Fremanezumab	Injection site reactions: pain, induration, erythema, pruritus, rash. Hypersensitivity reactions.

showed 61 cases of elevated blood pressure possibly related to erenumab. Majority of these patients were female (86%) with a median age of 56 years. Preexisting hypertension was present in 31% of the cases. Elevated BP was observed within a week of the first dose in 46% of the patients. Treatment for the elevated blood pressure was required in 44% of the patients.[50] This may be due to exposure of an at-risk population (elderly, hypertensive, and unstable cardiovascular disease) to erenumab. Also, the most recent summary of product characteristics for erenumab was updated to inform clinicians to warn patients about moderate to severe constipation on erenumab, which may have led to hospitalizations, and required surgery.

Finally, neutralizing antibodies have been found in small percentages in patients in the active groups of all trials. The presence of these antibodies however did not affect the clinical outcome as their titers were found to be very low.[51]

At this point in time, since all CGRP monoclonal antibodies have shown positive results in clinical trials on efficacy, tolerability, and safety, and since there is no head-to-head comparison from randomized clinical trials between the available molecules, there is no superior choice amongst the four different monoclonal antibodies for patients with episodic migraine. Clinicians should discuss with their patients the potential side-effects, routes of administration, and dosing scheme before starting a particular drug. Taking into account the cost of treatment, it is reasonable to start these drugs only in patients who have failed other evidence-based treatments for episodic migraine that are cheaper. There should also be a minimum of migraine days per month for these treatments to be cost-effective. For example, a person who has 1 migraine attack per year will probably not be a good beneficiary of this treatment, but a person who has multiple attacks per month will be. Therefore, since all studies had patients with migraine and a minimum of 4 headache days per month, this should be the minimum criterion for the start of these drugs in the real-world population. It is recommended to fulfill at least a 3-month period of appropriate dosing of the maximum tolerated dosage of one of the monoclonal antibodies to correctly evaluate its effect. If the treatment is beneficial, it should be continued for at least 6–12 months although treatment decisions should ideally be individualized.

Conclusion

CGRP pathway monoclonal antibodies are the first among a series of new therapeutic options being developed for the treatment of migraine. The main advantage of this new therapeutic mechanism is the specificity of the target unlike the nonspecific preventives previously available. The drugs are well tolerated with a very favorable side effect profile. Their route of administration and duration of action permits better compliance and adherence to therapy. The antibodies are particularly useful in patients who have already failed multiple preventive drugs or drug classes. They are also of use in medication overuse in patients with chronic migraine.[52,53] In addition, there is evidence of the benefit of galcanezumab in medication overuse in the setting of episodic migraine.[54] Another advantage seen with CGRP monoclonal antibodies is their quick onset of action – within the first week with erenumab, galcanezumab, and fremanezumab[39,55,56] and after 1 day with eptinezumab.[40] This is seen in stark contrast to the many months required for dose titration with current preventives. Eptinezumab, in particular, may have a role in an acute setting for status migrainosus, given its rapid onset of action. The use of these therapies can prevent the conversion of high-frequency episodic migraine to chronic migraine and can definitely improve the quality of life. It has the potential to address the unmet need for treatment of migraine if the limitation in the form of patient access can be overcome.

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Conflicts of interest
There are no conflicts of interest.

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