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General review

Monoclonal antibodies blocking CGRP transmission: An update on their added value in migraine prevention

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ABSTRACT

The avenue of effective migraine therapies blocking calcitonin gene-related peptide (CGRP) transmission is the successful outcome of 35 years of translational research. Developed after short-acting, small antagonists of the CGRP receptor (the ''gepants''), the monoclonal antibodies blocking CGRP or its receptor (CGRP/rec mAbs) have changed the paradigm in migraine treatment. Contrary to the classical acute medications like triptans or nonsteroidal anti-inflammatory drugs (NSAIDs) with a transient effect, they act for long durations exclusively in the peripheral portion of the trigeminovascular system and can thus be assimilated to a durable attack treatment, unlike the classical preventives that chiefly act upstream on the central facets of migraine pathophysiology. Randomized controlled trials (RCT) of eptinezumab, erenumab, fremanezumab and galcanezumab have included collectively several thousands of patients, making them the most extensively studied class of preventive migraine treatments. Their results clearly indicate that CGRP/rec mAbs are significantly superior to placebo and have been comprehensively reviewed by Dodick [Cephalalgia 2019;39(3):445-458]. In this review we will briefly summarize the placebo-subtracted outcomes and number-needed-to-treat (NNT) of these pivotal RCTs and analyze new and post-hoc studies published afterwards focusing on effect size, effect onset and sustainability, response in subgroups of patients, safety and tolerability, and cost-effectiveness. We will also summarize our limited real-world experience with one of the CGRP/rec mAbs. Although methodological differences and lack of direct comparative trials preclude any reliable comparison, the overall impression is that there are only minor differences in efficacy and tolerability profiles between the four monoclonals: the average placebo-subtracted 50% responder rates for reduction in migraine headaches are 21.4% in episodic migraine (NNTs: 4–5), 17.4% in chronic migraine (NNTs: 4–8). Patients with an improvement exceeding 50% are rare, chronic migraineurs with continuous headache are unlikely to be responders and migraine auras are not improved. The effect starts within the first week after administration and is quasi maximal at one month. It is sustained for long time periods and may last for several months after treatment termination. CGRP/rec mAbs are effective even after prior preventive treatment failures and in patients with medication overuse, but the effect size might be smaller. They significantly reduce disability and health care resource utilization. The adverse effect profile of CGRP/rec mAbs is close to that of placebo with few

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minor exceptions and despite concerns related to the safeguarding role of CGRP in ischemia, no treatment-related vascular adverse events have been reported to date. Putting the CGRP/rec mAbs in perspective with available preventive migraine drug treatments, their major advantage seems not to be chiefly their superior efficacy but their unprecedented efficacy over adverse event ratio. Regarding cost-effectiveness, preliminary pharmaco-economic analyses of erenumab suggest that it is cost-effective for chronic migraine compared to no treatment or to onabotulinumtoxinA, but likely not for episodic migraine unless attack frequency is high, indirect costs are considered and its price is lowered.

1. Introduction

Migraine has a considerable individual and societal impact. In spite of several decades of research, its therapeutic management remains imperfect. Migraine attack medications are ineffective in at least 30% of attacks, may be poorly tolerated and may even worsen the migraine disease if overused. The majority of migraine patients do not use migraine-specific medications, such as triptans, which in randomized controlled trials (RCTs) render patients pain-free after two hours in no more than 12–40% of attacks [1]. The efficacy rates of the preventive anti-migraine treatments are not superior: they are ineffective in 40–50% of patients and this, together with poor tolerance, explains why one in two chronic migraine sufferers abandons them after two months [2]. There is thus a real need for better-performing and better-tolerated treatments, particularly for migraine prevention.

One of the research pathways that has recently led to successfully enlarge the anti-migraine armamentarium is that of calcitonin-gene related peptide (CGRP). The present clinical use in migraine of drugs blocking CGRP neurotransmission is a paradigmatic example of the culmination of a transitional migraine research program that began in 1984.

The main steps are illustrated in Fig. 1. The discovery of CGRP in the trigeminovascular system was followed in 1990 by the demonstration of its increase in external jugular vein blood during migraine attacks and its normalization after treatment with sumatriptan. Together with the study showing that its intravenous administration induced migraine headaches in migraine sufferers, this made it a prime target for innovative therapeutic strategies. Following the characterization of the CGRP receptor-complex, non-peptide antagonists (“gepants”) were first developed and successfully used as attack treatment. Initially, their development was abandoned because of hepatotoxicity, but new gepants devoid of this toxicity were synthesized and will soon arrive on the market. In the meantime, monoclonal antibodies targeting CGRP or its receptor were produced and studied as a preventive treatment for migraine since 2013, leading to Food & Drug Administration (FDA) and European Medicines Agency (EMA) approvals in 2018 and 2019.

Since 2014, the literature has been submerged by the publications of the pivotal RCTs performed with the anti CGRP/rec monoclonal antibodies (CGRP/rec mAbs), by sub- or post-hoc analyses of these trials and by several meta-analyses. The RCTs have been criticized for their methodological heterogeneity, particularly with respect to the timing and period of the primary efficacy measures, but also for the way in which the results are presented, emphasizing the absolute decrease in number of migraine days from baseline, but not their relative decrease, persistent migraine days or placebo-subtracted results [3].

In 2019, Dodick published in *Cephalalgia* a comprehensive review of phase II-III RCTs of the four CGRP/rec mAbs currently available for episodic and chronic migraine: eptinezumab (Vyepti®), erenumab (Aimovig®), fremanezumab (Ajovy®) and galcanezumab (Emgality®) [4]. Our review will contain only a summary of the best published results for each antibody. By contrast, we will detail the studies published after Dodick’s review, i.e. mainly post-hoc analyses of pivotal trials on subgroups of patients, onset and persistence of effect, changes in quality of life and disability, as well as safety issues and side effects. Considering these data and our limited experience in clinical practice, we will discuss the added value of CGRP/rec mAbs compared to the published effects of conventional preventive treatments, although no comparative studies have been published to date. Before describing the clinical data, we will briefly summarize the neurobiological rationale subtending the anti-CGRP strategy and some pharmacological aspects. Both have been reviewed in extenso by others [5–7].

2. Neurobiological and pharmacological rationale

Migraine is considered to be a neurovascular disorder with a complex genetic predisposition. The primary pathophysiological events leading to an attack, on the one hand, occur in the central nervous system [8–10] and abnormal brain connectivity, reactivity and metabolism can be detected between attacks, chiefly in visual areas [11–15]. The migraine headache and some of its associated symptoms, on the other hand, originate in the so-called trigeminovascular system, i.e. the meningeal nociceptive afferents that belong in majority to the visceral portion of the 1st division of the trigeminal nerve and ganglion and surround dural and pial vessels [16,17]. The trigeminovascular system is the principal pain-signaling system of the viscera brain and comprises most molecular targets on which acute migraine drug treatments act, including 5-HT1B/D and 5-HT1F receptors, activated respectively by triptans and ditans (Fig. 2).

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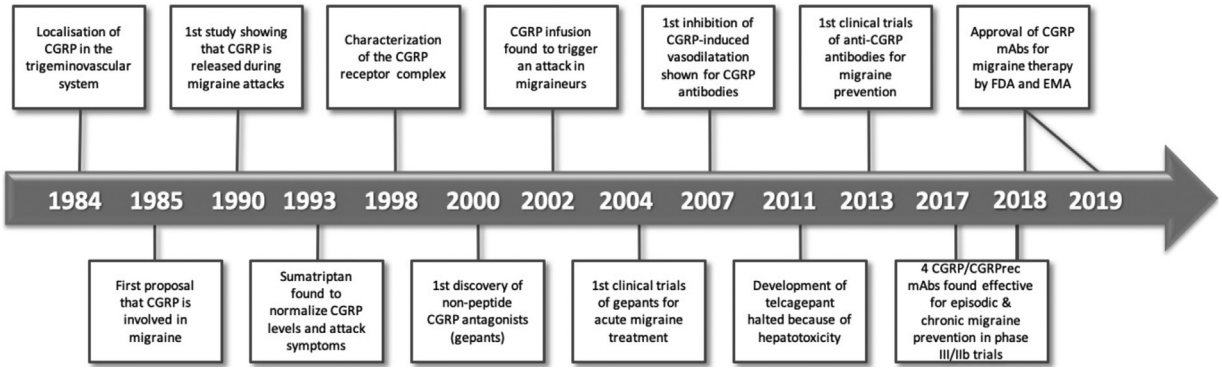

Fig. 1 – Timeline of translational research findings leading to CGRP/rec mAb therapy in migraine (modified after Edvinsson et al., 2018 [5]).

CGRP is a key player in the trigeminovascular system. The majority of nociceptive neurons in the Gasserian ganglion contain this neuropeptide and its receptor complex composed of a calcitonin-like receptor (CLR), a receptor activity-modifying protein 1 (RAMP1), and an intracellular receptor component protein (RCP), which increases cAMP levels activating protein kinase A (PKA), when CGRP binds to the receptor [18] (Fig. 3). One of the most likely mechanisms of action of triptans and ditans is to decrease CGRP release by activating the presynaptic 5-HT1D and 5-HT1F receptors respectively.

The avenue of CGRP/rec mAbs has changed the paradigm of migraine pharmacotherapy. The latter was classically subdivided into acute treatment (e.g. triptans, NSAIDs.) providing effective, though transient, relief in up to 70% of attacks, and preventive drugs (e.g. beta-blockers, anticonvulsants, calcium antagonists, antidepressants...) that decrease frequency and intensity of attacks on the long term in about 50% of patients, likely because of their central action. The difference in effect size between preventive and acute treatments may be due to the fact that the former are supposed to modify a large number of factors predisposing to migraine at the upper large entry of the ''pathophysiology funnel'', while the latter act at the level of the single common pathway of the migraine attack at the funnel's narrow end (Fig. 4).

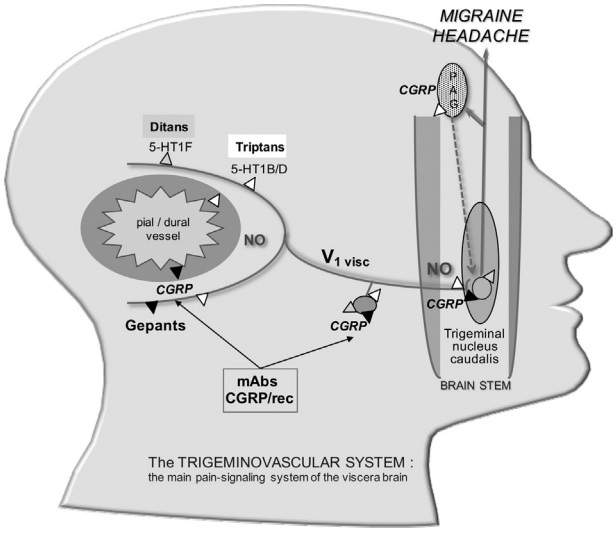

Fig. 2 – The trigeminovascular system thought to generate the migraine headache and some of its transmitter systems. The CGRP/rec mAbs are supposed to act in its peripheral portion (see text for details).

Because of their large molecular weight, CGRP/rec mAbs are thought to act outside of the brain and to block CGRP effects in the peripheral portion of the trigeminovascular system, i.e. at the funnel's exit. The difference with available acute medications, including the small molecules blocking the CGRP receptor, the gepants, is that the monoclonals have a very long half-live and exert their effect for several weeks [6]. They can thus be regarded as a ''durable attack treatment'' rather than a preventive treatment in the hitherto classical sense (Fig. 4). This might imply that they have no effect on migraine-associated symptoms due to factors located upstream in the pathophysiological cascade leading to the migraine attack, like the migraine aura, premonitory symptoms or interictal cognitive abnormalities. It should be kept in mind, however, that at the level of certain brain areas with an absent or less efficient blood-brain barrier, like the circumventricular organs and hypothalamic areas, the CGRP/rec mAbs might penetrate in sufficient amounts to exert a pharmacological effect [19,20].

The pharmacological profiles of the four available CGRP/rec mAbs studied in migraine are summarized in Table 1. Erenumab targets the CGRP receptor, and not the ligand like the three others, and is the only fully humanized antibody. The pharmacokinetics and dynamics of these mAbs are only partly understood. After subcutaneous injection, they are absorbed via the lymphatic system leading to a longer delay to maximal serum concentration compared to small molecules. They are eliminated via endocytosis and intracellular catabolism in the reticuloendothelial system of many organs. Compared to the others, fremanezumab seems to have a longer plasma half-life allowing for less frequent dosing. All CGRP mAbs are poorly immunogenic and they do not interfere with the immune system, unlike most monoclonal antibodies used in medicine [21].

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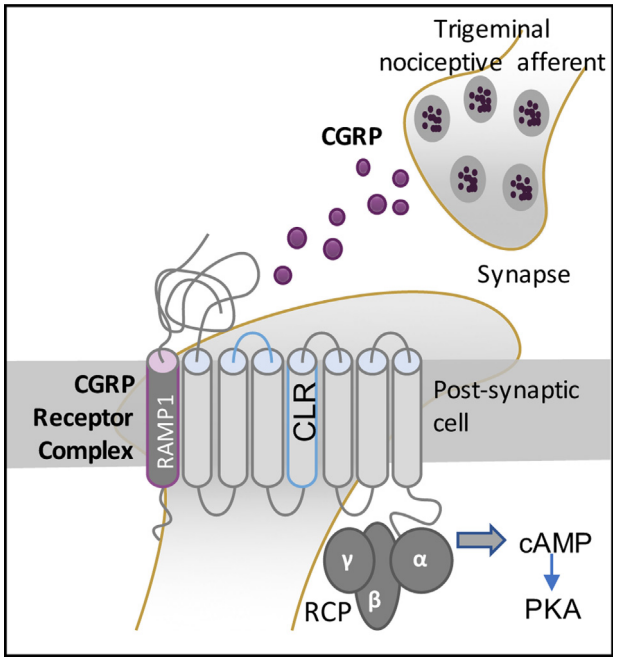

Fig. 3 – The CGRP receptor complex (modified after Pellesi L et al., 2017 [18]). CGRP, calcitonin gene-related peptide; CLR, calcitonin-like receptor; RAMP, receptor activity-modifying protein; RCP, receptor component protein; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A.

3. Efficacy data

3.1. *Pivotal Phase III/IIb RCTs*

At the time of Dodick's review (2019) [4] only the abstracts summarizing the effects of eptinezumab in episodic (EM) and chronic migraine (CM) were available. The RCT results are now published in extenso and illustrated in detail in Table 2 [22,23,24].

All RCTs of CGRP/rec mAbs have shown statistically significant improvements over placebo both in episodic and chronic migraine. A recent meta-analysis concludes that the average relative risk ratio versus placebo for 50% responder rates is 1.51 [25].

The RCTs are not directly comparable because of differences in methodology that could account for differences in outcomes. It seems nevertheless of interest to illustrate some of the results obtained for each of the four antibodies. Given the recent criticisms on the presentation of these results in the respective publications, we have calculated the therapeutic gain over placebo, number-needed-to-treat (NNT) and percentage decrease from baseline values for monthly migraine days.

The best results in pivotal phase III trials are summarized in Fig. 5 for 50% responder rate (≥ 50% decrease in monthly migraine days) in EM [23,26–28] and CM [24,29–31], and in Fig. 6 for the decrease in monthly migraine days in chronic migraine [24,29–31].

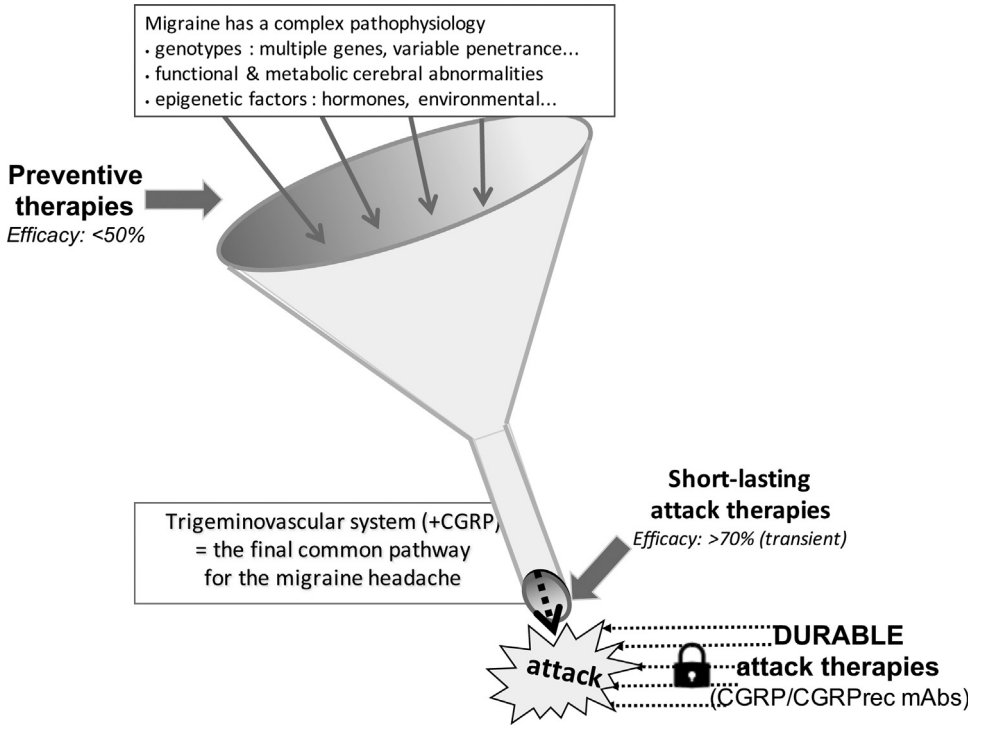

Fig. 4 – The "funnel model" of migraine etiopathogenesis and the paradigm change in migraine therapy (see text for explanations).

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Table 1 – Pharmacological profiles of the monoclonal antibodies against CGRP or its receptor.

	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Commercial name	**Vyepti**®	**Aimovig**®	**Ajovy**®	**Emgality**®
Ab IgG type	IgG1	IgG2	IgG2a	IgG4
Mode	Humanized	Human	Humanized	Humanized
Target	CGRP	CLR/RAMP1	CGRP	CGRP
Half-live (days)	28	28	45	27
Dosing in pivotal RCT	300 mg IV/3 months	70 or 140 mg SC/month	225 mg SC/month or 675 mg SC/3 months	240 mg SC (loading dose) 120 mg/month afterwards

Table 2 – Eptinezumab – recently published randomized placebo-controlled trials.

Reference	Migraine type & Nbr patients	Protocol	Outcome measures	Efficacy			Other
				Absolute	Therapeutic gain	NNT	
EPTINEZUMAB							
Dodick et al. 2019 [22] (phase IIb) (same as abstract by Smith et al., 2017 in Dodick 2019)	CM: *n* = 616	1:1:1:1:1	75% decrease in MMD over weeks 1–12, compared to 28-day baseline	Placebo 20.7%			HIT-6 score decreased by 10.0 for 300 mg compared to 5.8 for placebo
		Placebo 10 mg		10 mg 26.8% 30 mg 28.2%	6.10% 7.50%	16 13	AE rates similar to placebo
		30 mg 100 mg 300 mg	50% decrease in MMD	100 mg 31.4% 300 mg 33.3%	10.70% 12.60%	9 8	
		1 IV injection 12 weeks		Placebo 40.5% 10 mg 43.9% 30 mg. 55.6% 100 mg. 55.1% 300 mg. 57%	3.40% 15.10% 14.60% 16.50%	29 7 7 6	
Ashina et al. 2020 [23] (PROMISE I) (same as abstract by Saper et al., 2017 in Dodick 2019)	EM: *n* = 888	1:1:1:1	MMD decrease over weeks 1–12, compared to 4-w baseline	Placebo - 3.2 (– 24.3%)			Early discontinuation over 56 weeks:
		Placebo 30 mg	50% responder rate over weeks 1–12	30 mg – 4 (– 46%) 100 mg – 3.9 (– 45%)	21.70% 24.70%	5 4	Placebo 24.3% 30 mg 33.9%
		100 mg 300 mg		300 mg – 4.3 (– 50%)	25.70%	4	100 mg 20.4% 300 mg 19.4%
		1 IV injection/12 weeks 56 weeks: double-blind efficacity & safety (1–24 w); safety (24–32 w)		Placebo 37.4% 30 mg 50.2%	12.80%	8	No safety concerns
				100 mg 49.8%	12.40%	8	Most frequent treatment-emergent adverse events: nausea (1.6%), fatigue (1.4%)
				300 mg 56.3%	18.90%	5	Anti-drug antibodies: 15%(45% neutralizing)

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Table 2 (*Continued*)

Reference	Migraine type & Nbr patients	Protocol	Outcome measures	Efficacy			Other
				Absolute	Therapeutic gain	NNT	
Lipton et al. 2020 [24] (PROMISE II)	CM: *n* = 1,072	1:01:01	MMD decrease over weeks 1–12, compared to 4-w baseline	Placebo – 5.7 (– 35%)			Significant HIT-6 score decrease
		Placebo		100 mg – 7.6 (– 47%)	12%	8	
		100 mg	50% responder rate over weeks 1–12	300 mg – 8.2 (– 51%)	16%	6	Treatment-emergent AEs:
		300 mg 2 IV injection 12 weeks apart					Placebo: 7.9% Eptinezumab: 13.2% (1.7% hypersensitivity)
		32 weeks	75% responder rate over weeks 1–12	Placebo 39.3%			
				100 mg 57.6%	18.30%	6	
				300 mg 61.4%	22.10%	5	Anti-drug antibodies: 17% (21.4% neutralizing)
			Change from baseline in daily migraine in week 4				
				Placebo 15%			
				100 mg 26.7%	11.70%	9	
				300 mg 33.1%	18.10%	6	
				Placebo – 18.8%			
				100 mg – 27.1%	8.30%	12	
				300 mg – 29.8%	11%	9	

NNT: number-needed-to-treat; CM: chronic migraine; IV: intravenous; EM: episodic migraine; MMD: monthly migraine days; AE: adverse events; HIT-6: headache impact test.

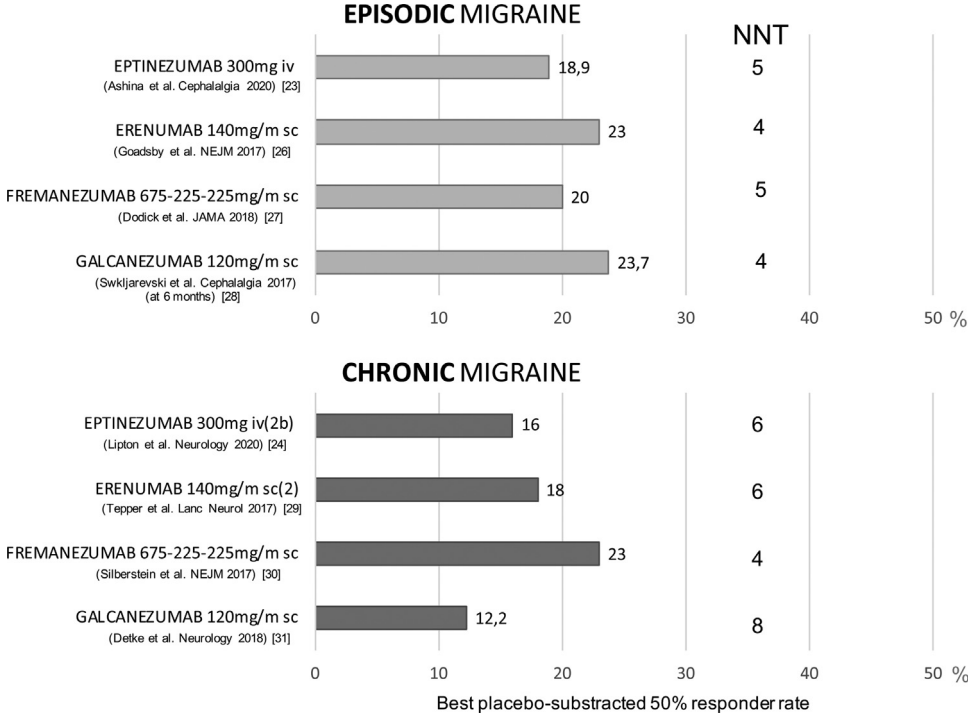

Fig. 5 – Best therapeutic gain (& number-needed-to-treat-NNT) for 50% responder rates at 3 months in episodic and chronic migraine.

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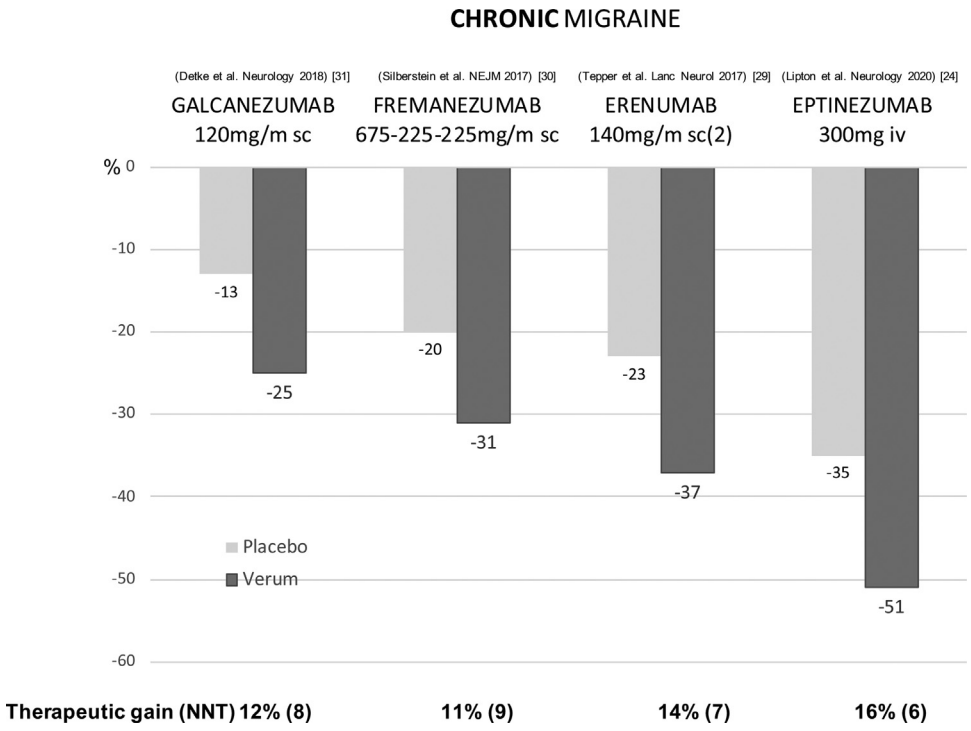

Fig. 6 – Best % decrease in monthly migraine days vs baseline and therapeutic gain (number-needed-to-treat).

There are some variations between compounds for placebo-subtracted 50% responder rates, especially for CM (18.9-23.7% in EM; 12.2-23% in CM). The range in NNT for 50% responders is narrow in episodic migraine (4–5), but somewhat larger in CM (4–8). Surprisingly, the mAb performing best in EM is the one that has the lowest performance in CM (Fig. 5).

There are even larger variations between drugs in the percentage decrease of monthly migraine days in CM (−25% to −50%). However, this could be due to a different placebo response, as therapeutic gains vary only between 11% and 16% and NNTs between 6 and 9. The greater variability of outcome in CM might be related in part to the heterogeneity of this group of patients (see below).

3.2. *Post-hoc and subgroup analyses*

Since the review by Dodick (2019) [4] post-hoc analyses were published for erenumab (Table 3), fremanezumab (Table 4) and galcanezumab (Table 5) regarding onset and sustainability of effects, influence of prior preventive treatment failures (including two dedicated trials, LIBERTY for erenumab and FOCUS for fremanezumab) and quality of life (including one original open label study). In addition, an RCT of erenumab was conducted in Japan [32] (Table 3). Taken together, these studies confirm that all CGRP/rec mAbs are superior to placebo for the prevention of migraine headaches including in high-frequency EM and CM whether patients have previously failed, or not, on one or several preventive treatments.

Supplementary aspects of the treatment results can be summarized as follows.

3.2.1. *75% and 100% responses*

A complete (100%) response to treatment is exceptional, not lasting or similar for placebo. The study of 100% responders to galcanezumab (Table 5) [33] was criticized for being misleading [34]. In CM, the placebo-subtracted 75% response rate was 13.1% (NNT:8) after three months for erenumab 140 mg/month (Table 3) [35], which is quasi equal to the 12.6% (NNT:8) over 12 weeks after 300 mg eptinezumab IV (Table 2) [22]. For fremanezumab 900 mg/month the placebo-subtracted 75% responder rate in CM was 9% (NNT:11), but this figure was sustained over the whole 3-month treatment period (Table 4) [36].

3.2.2. *Effect onset and sustainability*

Onset of effect for CGRP/rec mAbs occurs during the first week after dosing with similar placebo-subtracted 50% responder rates of 15.1% (NNT:7) and 15.4% (NNT:6) respectively in EM and CM for erenumab 140 mg/month (Table 3) [37]. For fremanezumab the percentage decrease from baseline in migraine headache days during the first week after one 675 mg dose is 37% (NNT:3) in high frequency EM [38] and 19% (NNT:5) in CM [39]. This effect size is very similar to those observed after 4 and 12 weeks (Table 4). During the first week of treatment with galcanezumab, the placebo-subtracted 50% responder rates were 20% (NNT:5) and 21% (NNT:5) after one injection of 150 mg [40] or 240 mg [41], which again are results very close to those obtained after 1 and 3 months of treatment (Table 5).

A 50% reduction in monthly migraine headache days is maintained over 3 months in EM with galcanezumab 120 or 240 mg/month (gain 20%; NNT:5) but less so over 6 months

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Table 3 – Erenumab–new RCTs and post-hoc analyses.

Reference	Migraine type & Nbr patients	Protocol	Outcome measures	Efficacy			Other
				Absolute	Therapeutic gain	NNT	
ERENUMAB							
Japanese patients							
Sakai et al. 2019 [32]	EM: *n* = 475	2:1:2:2	Monthly migraine days (MMD)	50% responders:			70 mg numerically superior to 140 mg
	MwoA: 74%	Placebo	50% responder rate (average months 4–6)	Plac 7.4%			
	MA: 26%	Erenumab 28 mg		70 mg 28.9%	21.50%	5	Similar AE profile in all groups
	(Japanese patients)	Erenumab 70 mg Erenumab 140 mg 1 SC inj/month 6 months		140 mg 27.2%	19.80%	5	
0–100% responders							
Brandes et al., 2019 [35] (post-hoc analysis from Tepper et al., 2017)	CM: *n* = 667	3:2:2	Monthly migraine days (MMD)	0% responders:			MMD reductions
		Placebo	0, 50, 75, 100% responder rate (3^{rd} month of double-blind phase)	Plac 28.1%			50% resp: –12.2 (70 mg) −12.5 (140 mg)
		Erenumab 70 mg		70 mg 16.3%			
		Erenumab 140 mg 1 SC inj/month 3 months		140 mg 20.9%			Overall: −2.6 (70 mg) −2.2 (140 mg)
				50% responders: Plac 23.5%			
				70 mg 39.9%	16.40%	6	
				140 mg 41.2%	17.70%	6	
				75% responders: Plac. 7.8%			
				70 mg 17.0%	9.20%	11	
				140 mg 20.9%	13.10%	8	
				100% responders: Plac 0.4%			
				70 mg. 4.3%	3.9% (ns)	26	
				140 mg. 2.7%	2.3% (ns)	43	
Effect onset							
Schwedt et al. 2018 [37] (post-hoc analysis from Goadsby et al., 2017 for EM & Tepper et al., 2017 for CM)	EM: *n* = 955	EM 1:1:1/CM 3:2:2	Weekly migraine days (WMD)	50% responders:			Occurrence of significance vs placebo within 1^{st} week (EM/CM):
	CM: *n* = 667	Placebo Erenumab 70 mg Erenumab 140 mg 1 SC inj/month 3 months	50% responders (week 1)	Week 1 (EM/CM) Plac 27.5%/16%			70 mg day 7/day 6 140 mg day 3/day 7
				70 mg 33.7%(ns)/ 25.5%	6.2/9.5%	16/11	
				140 mg 42.6%/ 31.4%	15.1/15.4%	7/6	

Table 3 (*Continued*)

Reference	Migraine type & Nbr patients	Protocol	Outcome measures	Efficacy			Other
				Absolute	Therapeutic gain	NNT	
Influence of prior preventive treatment failure							
Reuter et al., 2018 [43] (LIBERTY)	EM: *n* = 246 (MwoA, MA–35%) Prior failure of 2–4 preventive treatments	1:01 Placebo Erenumab 140 mg 1 SC inj/month 3 months	Monthly migraine days (MMD) 50% responder rate (3rd month of double-blind phase)	50% responders: Plac 14% 140 mg 30%	16%	6	Tolerability & safety: Erenumab ≈ placebo (most frequent: injection site pain)
Ashina et al. 2018 [45] (subanalysis of Tepper et al., 2017)	CM: *n* = 492 Prior preventive treatment: 1) none (*n* = 214) 2) > 1 (*n* = 453) 3) > 2 (*n* = 327)	2:01:01 Placebo (*n* = 286) 70 mg (*n* = 191) 140 mg (*n* = 190) 1 SC inj/month 3 months	Change from baseline in MMD during month 3 in the 3 subgroups	MMD decrease vs placebo 1) 70 mg: −2.2; 140 mg: −0.5 [n.s.] 2) 70 mg: −2.5;140 mg: −3.3 3) 70 mg: −2.7;140 mg: −4.3			Incidence of adverse events: 1/3 of group 1 patients, 1/2 of groups 2 & 3; discontinuation due to AE: 2 with erenumab, 2 with placebo
			50% responders for MMD reduction	1) placebo 38.1%	11.9%	8	
				70 mg 50.0% [n.s.]			
				140 mg 41.9% [n.s.]	3.8%	26	
				2) placebo 17.5%			
				70 mg 34.7%	17.2%	6	
				140 mg 40.8%	23.3%	4	
				3) placebo 14.2%			
				70 mg 35.6%	21.4%	5	
				140 mg 41.3%	27.1%	4	
Goadsby et al. 2019 [46] (subanalysis of STRIVE phase III RCT by Goadsby et al., 2017)	EM: *n* = 955 Prior preventive treatment: 1) none (*n* = 550) 2) > 1 (*n* = 370) 3) > 2 (*n* = 161)	1:01:01 Placebo (*n* = 138) 70 mg (*n* = 139) 140 mg (*n* = 128) 1 SC inj/month 6 months	Change from baseline in monthly migraine days (MMD) during months 4–6 in the 3 subgroups	MMD decrease vs placebo 1) 70 mg: −0.9;140 mg: −1.3 2) 70 mg: −2.0;140 mg: −2.5 3) 70 mg: −1.3;140 mg: −2.7			Incidence of adverse events: half of group 1 patients, 2/3 of groups 2 & 3; discontinuation due to AE: 0–6.9%
			50% responders for MMD reduction	1) placebo 32.6%			
				70 mg 46.5%			
				140 mg. 55.0%	13.90%	7	
				2) placebo 17.5%	22.40%	4	
				70 mg 38.6%			
				140 mg 39.7%	21.10%	5	
				3) placebo 11.1%	22.20%	5	
				70 mg 26.5%			
				140 mg 36.2%	15.40%	6	
					25.10%	4	
Influence of acute medication overuse							
Tepper et al. 2019 [50]	CM: *n* = 667 Medication overusers: *n* = 274 (41%)	3:02:02 Placebo (*n* = 117) 70 mg (*n* = 79) 140 mg (*n* = 78) 1 SC inj/month 3 months	Change from baseline in MMD (month 3) 50% responders for MMD reduction	Placebo −3.5 (−18%)			Patients (%) transitioning from overuse to non-overuse status at mth 3 (Placebo/140 mg): Simple analgesics: 52/71
				70 mg −6.6 (−35%)	17%	6	

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Table 3 (*Continued*)

Reference	Migraine type & Nbr patients	Protocol	Outcome measures	Efficacy			Other
				Absolute	Therapeutic gain	NNT	
				140 mg −6.6 (−35%)	17%	6	Triptans: 33/54 Combination: 40/59
				Placebo 18%			
				70 mg 36%	18%	6	
				140 mg. 35%	17%	6	
Effect on disability and quality of life							
Buse et al. 2018 [52] (subanalysis of STRIVE phase III RCT by Goadsby et al., 2017)	EM: *n* = 955	1:01:01	Change from baseline in disability and quality of life (months 4–6):	mMIDAS:			Erenumab-induced changes were significant as early as month 1.
		Placebo (*n* = 319)	→monthly MIDAS, 3-month MIDAS	Placebo −4.6			
		70 mg (*n* = 317)		70 mg −6.7	−2.1		
		140 mg (*n* = 319)		140 mg −7.5	−2.8		
		1 SC inj/month	→HIT-6	Severe 3-mth MIDAS(> 21)			
		6 months		Placebo 51.6%			
				70 mg 38.5%	13.10%	8	
				140 mg 31.1%	19.50%	5	
				HIT-6:			
				Placebo −4.6			
				70 mg −6.7	−2.1		
				140 mg −6.9	−2.3		
			→MSQ (RFR, RFP, EF)	MSQ (RFR/RFP/EF)			
				Placebo +11.7/8.5/7.7			
				70 mg +16.8/12.7/12.9	0.233516		
				140 mg +18.1/13.9/14.4	0.179657		

NNT: number-needed-to-treat; EM: episodic migraine; MwoA: migraine without aura; MA: migraine with aura; SC: subcutaneous; AE: adverse events; MMD: monthly migraine days; WMD: weekly migraine days; MIDAS: migraine disability assessment, HIT-6: headache impact test, MSQ: migraine specific quality of life questionnaires; RFR: role function-restrictive; RFP: role function-preventive; EF: emotional function.

(gain 12.5%; NNT:8) [42]; in CM the placebo-subtracted sustained 50% responder rates over 3 months are 10.5% and 8.3% for 120 mg and 240 mg [42] but 22% for 150 mg [40] (Table 5). A placebo-subtracted 50% response rate of 25% (NNT: 4) is sustained for 3 months with fremanezumab 675 mg/month in high frequency EM, but it is only of 6% (NNT:17) in CM [36].

3.2.3. *Influence of migraine severity and prior preventive treatment failure*

Two RCTs were specifically designed to analyze the influence of multiple previous preventive treatment failures, the LIBERTY trial for erenumab [43] and the FOCUS trial for fremanezumab [44]. Both show that the more difficult and more severely affected patients respond to treatment. The 50% responder rate is higher in FOCUS (25% placebo-subtracted) than in LIBERTY (16%), but the former included both EM and CM patients, the latter only EM patients among whom 35% with aura (Tables 3 and 4). Both in CM [45] and EM [46], outcome with erenumab was not very different between patients who never had a preventive treatment (the majority in CM, a minority in EM) and those who had tried at least one or two preventives, except that the placebo response was almost doubled in the former group. Surprisingly so, in the REGAIN trial of galcanezumab the outcome over three months of treatment in patients subgroups with no, one or several prior failures of preventive treatment differs between the two doses administered: with the 120 mg/month dose the placebo-subtracted 50% responder rate is highest for 2 prior failures (20.2%; NNT:5) and lowest for no prior failure (4%; NNT:25), while the opposite is reported with the 240 mg/month dose where corresponding values are 9.3% (NNT: 11) for 2 prior failures and 15.5% (NNT: 6) for no prior failure [47]. In patients who previously failed on onabotulinumtoxinA and participa-

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Table 4 – Fremanezumab–new RCT and post-hoc analyses.

Reference	Migraine type & Nbr patients	Protocol	Outcome measures	Efficacy			Other
				Absolute	Therapeutic gain	NNT	
FREMANEZUMAB							
Effect onset & sustainability							
Silberstein et al., 2018 [38] (post-hoc analysis of Bigal et al., 2015a)	HFEM: *n* = 297	1:01:01	Decrease in weekly MHD during the 1st 3 weeks	Week 1:			Similar early reductions in headache hours, associated symptoms and acute medication use
		1) 225 mg/mth 2) 675 mg/mth 3) placebo 1 SC inj/mth for 3 mths		1) −1.28 (−44%) 2) −1.38 (−49%) 3) −0.36 (−12%)	32% 37%	3 3	
				Week 2:			
				1) −1.20 (−41%) 2) −1.24 (−44%) 3) −0.44 (−15%)	26% 29%	4 3	
				Week 3:			
				1) −1.16 (−40%) 2) −1.17 (−42%) 3) −0.52 (−18%)	22% 24%	5 4	
Winner et al. 2019 [39] (post-hoc analysis of Silberstein et al., 2017-HALO trial)	CM: *n* = 1130	1:01:01	Onset of efficacy: change in headache days during the 1st 4 weeks	Headache days of at least moderate severity in the 4-week period after 1st 675 mg dose			Separation of all-fremanezumab group from placebo by day 2 after 1st dose
		1) 675 mg mth 1; placebo mths 2–3 (*n* = 376) 2) 675 mg mth 1; 225 mg mths 2–3 (*n* = 379) 3) placebo mths 1,2,3 (*n* = 375) 1 SC inj/mth for 3 mths		1 + 2) – 4.6 (−35%) 3) – 2.3 (−17%) Week 1 after 1st dose 1 + 2) – 1.1 (−34%) 3) – 0.5 (−15%)	18% 19%	6 5	
				Over 12 weeks			
				1) – 4.3 (−33%) 2) – 4.6 (−36%) 3) – 2.5 (−19%)	14% 17%	7 6	
Halker Singh et al. 2018 [36] (post-hoc analysis of Bigal et al., 2015a,b)	Total: *n* = 560	1:01:01	Sustained 50%, 75%, 100% reductions for 3 months in MMD, moderate/severe headaches and acute medication use	50%/75% resp for MMD:			Similar reductions in moderate-to-severe headaches and acute medication use
	HFEM: *n* = 297 CM: *n* = 264	HFEM 1) 225 mg/mth 2) 675 mg/mth 3) placebo 1 SC inj/mth for 3 mths CM 1)675 mg/225 mg/ 225 mg 2) 900 mg/mth 3) placebo 1 SC inj/mth for 3 mths			HFEM 1) 39%/19% 2) 35%/11% 3) 10%/3% CM	29%/16% 25%/8%	3/6 4/13	Rare 100% responders: 3/293 in the 2 placebo groups,

Table 4 (*Continued*)

Reference	Migraine type & Nbr patients	Protocol	Outcome measures	Efficacy			Other
				Absolute	Therapeutic gain	NNT	
				1) 24% (ns)/7% (ns)	6%/4%	17/25	
				2) 33%/12%	15%/9%	7/11	11/363 in the 4 fremanezumab groups
				3) 18%/3%			
Influence of prior preventive treatment failure							
Ferrari et al., 2019 [44] (FOCUS)	Total (MwoA & MA):*n* = 838	1:01:01	1) Monthly migraine days (MMD)	MMD % decrease (mean over 3 mths) (EM + MC):			Therapeutic gain similar in EM and CM
	EM: *n* = 329	1) 675 mg mth 1; placebo mths 2–3		1) Quarterly −34.9%			
	CM: *n* = 509	2) 225 mg (EM) or 675 mg (CM) mth 1; 225 mg mths 2–3		2) Monthly −36.8%	26.40%	4	Significant MMD reduction during 1st month in 1) & 2)
	Previous failure of 2–4 preventive treatments	3) placebo mths 1,2,3, 1 SC inj/mth 3 mths		3) Plac −8.5%	28.30%	4	
			2) 50% responder rate (average of 3-mth double-blind phase)	50% resp			
				1) Quarterly 34%	25%	4	AE rate similar for fremanezumab and placebo
				2) Monthly 34%	25%	4	
				3) Placebo. 9%			
Functional performance on headache-free days							
VanderPluym et al. 2018 [53] (post-hoc analysis of Bigal et al., 2015a,b)	Total: *n* = 560	1:01:01 HFEM 1) 225 mg/mth 2) 675 mg/mth 3) placebo 1 SC inj/mth for 3 mths CM 1) 675 mg/225 mg/225 mg 2) 900 mg/mth 3) placebo 1 SC inj/mth for 3 mths	Functional performance on headache-free days	Change from baseline in total headache-free days/headache-free days with normal function at month 3:			Improvement on all measures of functional performance on headache-free days in fremanezumab groups
	HFEM: *n* = 297			HFEM			
	CM: *n* = 264			1) 6.8/4.76	2.8/3.16		
				2) 6.4/4.34	2.4/2.74		
				3) 4.0/1.60			
				CM			
				1) 8.1/4.34	2.7/0.86		
				2) 8.3/6.05	2.9/2.57		
				3) 5.4/3.48			

ted in the three pivotal RCTs of galcanezumab, outcome is better than in the other patients: placebo-subtracted 50% response 31.9% (NNT: 3) for 120 mg, 38.1% (NNT: 3) for 240 mg [48].

In EM patients with high attack frequency, the response to galcanezumab, though superior to placebo, is slightly lower than in those with low frequency [49] (Table 5).

In a CM subgroup of acute medication overusers, the response rates to 70 or 140 mg/month erenumab are comparable to those seen in patients without medication overuse [50] (Table 3).

3.2.4. *Effect on disability and healthcare resource utilization*

Several post-hoc studies report significant improvements in quality of life and disability scales during treatment with

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Table 5 – Galcanezumab–post-hoc analyses and open label study.

Trial & reference	Migraine subtype & Nbr patients	Protocol	Outcome measures	Efficacy			Other
				Absolute	Therapeutic gain	NNT	
GALCANEZUMAB							
100% responders							
Rosen et al., 2018 [33] (post-hoc analysis of phase 3 RCT trials EVOLVE-1 & EVOLVE-2)	EM: *n* = 1739	2:01:01	1) Mean monthly 100% response rate on an average month	1) Placebo 5.9%			More patients with a 100% monthly response in the last 3 months of the 6-month double-blind phase
		Placebo (*n* = 875) 120 mg (*n* = 436) 240 mg (*n* = 428) 1 SC inj/month 6 months	2. 100% response for: – at least 1 month – at least 3 months – all 6 months	120 mg 13.5% 240 mg 14.3%	7.60% 8.40%	13 12	Average time between non-consecutive migraine headache days: 1 month for patients with at least a 1-month 100% response.
				2) 1 month: Placebo 19.5% 120 mg 38.8% 240 mg 41.6% 3 months: Placebo 5.5% 120 mg 10.6% 240 mg 13.8% 6 months: Placebo 0.2% 120 mg 0.7% (ns) 240 mg. 1.4%	 19.30% 22.10% 5.10% 8.30% 0.50% 1.20%	 5 5 20 12 200 83	
Effect onset and sustainability							
Goadsby et al., 2019 [40] (post-hoc analysis of phase II-a RCT by Dodick et al., 2017)	EM: *n* = 204	1:01	1) mean reduction of MHD at week 1	1) Plac −0.53 150 mg −0.89	−0.36		
		Placebo (*n* = 105)	2) 50% responder rate for MHD at week 1	2) Plac 42% 150 mg 62%	20%	5	
		150 mg (*n* = 99)	3) 50% responder rate at month 1 sustained at months 2 and 3	3) Plac. 25% 150 mg 47%	22%	5	
		SC inj biweekly	4) Subsequent 50% response at months 2 and 3 in non-responders at month 1	4) Plac 20% (*n* = 61) 150 mg 27% (*n* = 41) (ns)	7%	14	
		3 months	5) Subsequent 50% response at month 3 in non-responders at months 1 and 2	5) Plac 24% (*n* = 46) 150 mg 50% (*n* = 22)	26%	4	
Detke et al. 2019 [41] (post-hoc analysis of EVOLVE-1 & EVOLVE-2)	EM: *n* = 1773	2:01:01	1) month of effect onset	1) month 1:			Earliest effect onset on day 1 after 1st dose

Table 5 (*Continued*)

Trial & reference	Migraine subtype & Nbr patients	Protocol	Outcome measures	Efficacy			Other
				Absolute	Therapeutic gain	NNT	
		Placebo (n = 894)	– decrease in MHD	Evolve-1 Evolve-2			
		120 mg (with 240 mg loading dose) (n = 444)		Placebo. −1.67(18%) −1.17(13%)			
		240 mg (n = 435)		120 mg. −3.72(41%) −3.90(43%)	23%/30%	4/3	
		1 SC/month		240 mg −3.59(39%) −3.23(35%)	21%/22%	5/5	
		6 months	2) week of effect onset	2) week 1:			
			– decrease in MHD	Evolve-1. Evolve-2 Placebo. −0.35(17%) −0.47(22%)			
			– 50% response	120 + 240 −0.94(45%) −1.05(50%)	28%/28%	4/4	
				Placebo. 32.4%. 38%			
				120 + 240 mg 54.3%. 59.4%	21.9%/21.4%	5/5	
Förderreuther et al., 2018 [42] (post-hoc analysis of phase 3 RCT trials EVOLVE-1, EVOLVE-2 & REGAIN)	EM: n = 1773	2:1:1 (EM/CM)	Maintenance of 50% reduction in monthly MHD	EM: ≥ 3 consecutive months:			AE: Injection-site reaction (pain, erythema, pruritus, swelling)
	CM: n = 1113	Plac (n = 894/558)	EM:	Placebo 21%			
		120 mg (with 240 mg loading dose) (n = 444/278)	≥ 3 consecutive months	120 mg 41.5%	20.5%	5	
		240 mg (n = 435/277)	6 consecutive months	240 mg 41.1%	20.1%	5	
		1 SC/month	CM:	EM: 6 consecutive months:			
		6 months (EM)	3 consecutive months	Placebo 8%			
		3 months (CM)		120 mg 19%	11%	9	
				240 mg 20.5%	12.5%	8	
				CM: 3 consecutive months:			
				Placebo 6.3%			
				120 mg 16.8%	10.5%	10	
				240 mg 14.6%	8.3%	12	
Influence of attack frequency & prior preventive treatment failure							
Silberstein et al., 2019 [49] (post-hoc analysis of phase 3 RCT trials EVOLVE-1 & EVOLVE-2)	EM: n = 1773:	2:01:01	1) Mean reduction of monthly MHD over months 1–6	1) LFEM: Plac – 0.9 (−15.5%)			No significant difference between LFEM and HFEM

Table 5 (*Continued*)

Trial & reference	Migraine subtype & Nbr patients	Protocol	Outcome measures	Efficacy			Other
				Absolute	Therapeutic gain	NNT	
	LFEM (n = 597–34%): 4–7 MMD vs HFEM (n = 597–66%): 8–14 MMD	Placebo		120 mg −2.8 (−48%)	32.50%	3	
		120 mg		240 mg −2.3 (−40%)	24.50%	4	
		240 mg		HFEM: Plac −3.4 (−31%)			Significant decrease in disability scores in both groups
		1 SC inj/month	2) 50% responder rate	120 mg −5.4 (−50%)	19%	5	
		6 months		240 mg −5.5 (−51%)	20%	5	
				2) LFEM: Plac 38%			
				120 mg 63%	25%	4	
				240 mg 55%	17%	6	
				HFEM: Plac. 39%			
				120 mg 60%	21%	5	
				240 mg 61%	22%	5	
Ruff et al., 2019 [47] (post-hoc analysis of RCT REGAIN)	CM: n = 1113 Prior preventive treatment: 77.8% > 1 failure: 51.5% > 2 failures: 31.2% > 3 failures: 17.9%	1:01:01 Placebo (n = 558) 120 mg (n = 278) 240 mg (n = 277) 1 SC inj/month 3 months	1) Mean reduction of monthly MHD over months 1–3	1) > 2 prior failures: Plac −1.01 (−5%)			Migraine-Specific Quality of Life Questionnaire - Role Function Restrictive domain score significantly improved
				120 mg −5.35 (−27%)	22%	5	if ≥ 1 or ≥ 2 failures with 120 mg and 240 mg, if no previous failure only with 240 mg.
				240 mg −2.77 (−15%)	10%	10	
				> 1 prior failure: Plac −2.02 (−10%)			
				120 mg −5.53 (−28%)	18%	6	
				240 mg −3.53 (−18%)	8%	13	
				No prior failure: Plac. −4.28 (−22%)			
				120 mg −4.88 (−26%) (ns)	4%	25	
				240 mg −6.58 (−34%)	12%	8	
			2) 50% responder rate	2) > 2 prior failures: Plac 9.4%			
				120 mg 29.6%	20.2%	5	
				240 mg 18.7%	9.3%	11	
				> 1 prior failure: Plac 11.3%			
				120 mg 31.2%	19.9%	5	
				240 mg 20.5%	9.2%	11	
				No prior failure: Plac 19.9%			
				120 mg 23.9% (ns)	4%	25	

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Table 5 (*Continued*)

Trial & reference	Migraine subtype & Nbr patients	Protocol	Outcome measures	Efficacy			Other
				Absolute	Therapeutic gain	NNT	
				240 mg 35.4%	15.5%	6	
Ailani et al. 2019 [48] (post-hoc analysis of phase 3 RCT trials EVOLVE-1, EVOLVE-2 & REGAIN)	EM: *n* = 1773	2:01:01	1) Mean reduction of monthly MHD over months 1–3	1) Placebo −0.88			Significant decrease in MHD with acute medication use
	CM: *n* = 1113	Plac		120 mg. −3.91	3.03		Significant improvement in MSQ Role Function-Restrictive scores
		120 mg (with 240 mg loading dose)	2) 50% response over months 1–3	240 mg −5.27	4.39		
	Onabotulinum-toxinA Failure (*n* = 129)	240 mg 1 SC/month 6 months (EM) 3 months (CM)		2) Placebo. 9.4% 120 mg 41.3% 240 mg. 47.5%	31.90% 38.10%	3 3	
Patient satisfaction & effect on health care resource utilization							
Ford et al. 2018 [51]	Total: *n* = 270	Open label study	1) Patient satisfaction	1) 69% (120 & 240 mg)			Patient satisfaction increased with duration of treatment
	EM: *n* = 213 CM: *n* = 57 (MA not specified; no prior preventive treatment in 37.4% of patients)	120 mg (*n* = 135) (after 1st loading dose of 240 mg) 240 mg (N = 135) 1 SC inj/month 12 months	2) Reduction of Health care resource utilization (HCRU) (per 100 person-years)	2) HCRU Health care professional visits: from 173.4 to 59.6; Emergency room visits: from 20.2 to 4.7 (ns for 120 mg); Hospital admissions: from 3.7 to 0.4			81% of satisfied patients were so because of less side effects
			3) Overall MMD reduction from baseline	3) EM: − 5,1 (120 mg); − 6,1 (240 mg) CM: − 7,2 (120 mg); − 8,2 (240 mg)			
			4) Overall reduction from baseline in MMD with acute medication	4) – 5.1 (120 & 240 mg)			

NNT: number-needed-to-treat; EM: episodic migraine; SC: subcutaneous; MHD: migraine headache days; CM: chronic migraine; AE; adverse events; HFEM: high frequency episodic migraine; LFEM: low frequency episodic migraine; MA: migraine with aura; MMD: monthly migraine days.

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Table 6 – Erenumab–subanalyses of safety and tolerability.

Reference	Migraine type & Nbr of patients	Protocol	Outcome measures	Adverse events	Other
ERENUMAB					
Ashina et al., 2019 [54] (pooled analysis of 4 RCTs)	n = 2443: double-blind EM: n = 1783 CM: n = 660 (received at least 1 dose) n = 2375: long term extension	Placebo Erenumab 70 mg Erenumab 140 mg 1 SC inj/month Cumulative exposure: 2641.2 patient-years	Safety 1) Double-blind phase 2) Open-label extension (> 3 years)	Exposure-adjusted adverse event rate. 1) AE rate/100 patient-years similar to placebo, except Inj site reactions (17.1 vs 10.8), constipation (7.0 vs 3.8), muscle spasm (2.3 vs 1.2) 2) Similar, but lower rates	No cardiovascular AE Anti-drug antibodies 70 mg: 56/885 (6.3%) (3 neutralizing) 140 mg: 13/504 (2.6%)
Ashina et al., 2019 [55] (interim analysis of open-label treatment phase-OLTP- of RCT by Sun et al., 2016)	EM: n = 250	OLTP for 2 years at 70 mg (n = 383) followed by 1 year at 140 mg (n = 250)	Safety & tolerability	132 (34.5%) patients discontinued OLTP before 3rd year Exposure-adjusted rate per 100 patient-years (n = 250): →all AE: 128.1 (placebo phase: 350.1) →AE leading to discontinuation: 0.3 →vascular events: 0.0 →hepatotoxicity: 0.0	Non-neutralizing antibodies: n = 2 (transient)
Kudrow et al. 2019 [56] (pooled analysis of 4 RCTs)	n = 2443 EM & CM MA: 46%	Placebo (n = 1043) Erenumab 70 mg (n = 893) Erenumab 140 mg (n = 507) 1 SC inj/month 3 or 6 months + OLTP	Vascular safety Total exposure to 70/140 mg: 2639 patient-years	> 2 vascular risk factors →Any AE rate: Plac. 54.2% 70 mg 48.4% 140 mg 55% →Serious AE rate: Plac. 1.9% 70 mg. 2.5% 140 mg. 1.3%	4 adjudicated cardiovascular events during erenumab OLTP: →2 deaths (coronary arteriosclerosis & genetic arrhythmogenic cardiomyopathy →2 vascular events

EM: episodic migraine; CM: chronic migraine; SC: subcutaneous; AE: adverse events; OLTP: open-label treatment phase; MA: migraine with aura.

CGRP/rec mAbs. One open label trial of galcanezumab [51] comprising both EM and CM patients found that 69% of patients were still satisfied with the treatment after 12 months (81% because of less side effects) and utilized significantly less healthcare resources (Table 5). Similarly, MIDAS, HIT-6 and MSQ scores were significantly improved on sub-analysis of the erenumab Strive RCT [52] (Table 3), while increase of headache-free days was associated with better functional performance on these days after 3 months treatment with fremanezumab [53] (Table 4).

4. Safety and tolerability

In none of the CGRP/rec mAbs studies there have been safety concerns and the adverse event profile is globally considered to be similar to that of placebo. Three studies of erenumab have analyzed in detail adverse event rate and type, vascular safety and anti-drug antibodies (Table 6). Except for injection site reactions (17.1% vs 10.8% for placebo), constipation (7% vs 3.8%) and muscle spasms (2.3% vs 1.2%), the adverse event rate was not superior to that of placebo, both during the double-blind phase and the 3-year open-label extension [54]. Anti-drug antibodies were found in 6.3% of 885 patients for the 70 mg dose, in 2.6% of 504 patients for 140 mg. In 132 patients treated with erenumab for three years, there were no vascular events or hepatotoxicity [55]. In a pooled analysis of four RCTs with erenumab, the vascular safety profile was comparable to that of placebo [56].

5. Personal experience

In our headache clinic we have treated 150 migraine patients (82 EM, 48 CM) with one of the CGRP/rec mAbs. To be eligible for treatment, the patients had to have at least four migraine days per month and at least two prior preventive treatment failures, among which a beta-blocker (unless contraindicated).

Outcome at 6 months has been analyzed up to now for 113 patients (72 EM, 41 CM). For regulatory reasons, the full results cannot be disclosed at the present time. Let us mention, nonetheless, that the 50% responder rate for monthly migraine days was globally 56%, which is close to the non-placebo-subtracted values in the above described RCTs. In chronic migraine, however, the 50% responder rate was only 29%, quite below the RCT data. Sub-analyzing the chronic migraine cohort, we found that only 14% of patients with continuous headache (ICHD3 A1.3.2) (n = 21) responded to the

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treatment, while the 50% responder rate was 45% in chronic migraine with pain-free periods (ICHD3 A1.3.1) ($n = 20$).

The 50% responder rate was lower in patients with more than 2 prior preventive treatment failures: 65.5% in patients with 2 failures ($n = 29$), 40.5% in those with more than 2 failures ($n = 84$).

In patients having both migraine attacks with and without aura there was a significant decrease in monthly migraine days, but not in frequency of attacks with aura.

Tolerance was excellent overall with 34% of patients reporting minor probably treatment-related adverse effects, more than half of them complaining of new onset, or most frequently, worsening of constipation (19%).

After 3 months, 13 out of 113 patients abandoned the treatment because of inefficacy; at 6 months 10 additional subjects did so, resulting in a 20% discontinuation rate over 6 months.

6. Conclusions and open questions

According to the results of the pivotal RCTs and post-analyses there is no doubt that CGRP/rec mAbs are effective preventive therapies for migraine, both regarding attack frequency and disability or quality of life. There remains nevertheless a number of unsolved questions and uncertainties.

6.1. *Efficacy*

The subtle differences in outcome between compounds are likely due to methodological differences, but cannot be evaluated objectively due to the lack of comparative studies. Meanwhile a recent meta-analysis of 11 RCTs found no significant difference in efficacy and safety results between erenumab, fremanezumab and galcanezumab [25]. This does not exclude, however, that, like for the oral triptans in acute migraine therapy, individual differences in effectiveness may exist for the four CGRP/rec mAbs.

Although their efficacy tends to weaken with severity of the migraine disease, it remains significant in the most disabled patients, besides those with continuous headache. This was previously reported also for other preventive treatments [57,58] and supports the concept that chronic migraine patients with pain-free periods and those with continuous pain represent two distinct clinical, and likely pathophysiological, subgroups, which, by corollary, suggests that they may need different management strategies.

As surmised on the basis of their inability to cross the blood-brain barrier, the CGRP/rec mAbs do not seem to improve migraine aura. Such difference in effect between migraine types is not the rule for other preventive therapies, with the notable exception of lamotrigine that is effective in migraine with aura, but not in migraine without aura [59]. What distinguishes responders and non-responders to CGRP/rec mAbs in patient groups with the same clinical profile is still an open question. In a small study of 10 responders and three non-responders to erenumab, a higher susceptibility to attack induction by CGRP was found in responders [60]. It also remains to be determined if non-responders to the receptor-blocking erenumab may benefit from a switch to a ligand-blocking mAb, as recently suggested [61], and if switching between the latter could help some patients.

The effect onset is quasi-maximal one month after administration of a CGRP/rec mAb, although outcome continues to improve slightly up to 12 months and beyond, as shown for erenumab [54]. However, for galcanezumab [40], only a small proportion of patients not responding during the 1st month did so in the 2nd or 3rd month. Interestingly, it was shown for erenumab and galcanezumab that the beneficial effects remain unchanged for at least 12 weeks after treatment termination [62]. There is at present no clear consensus on when to stop treatment because of inefficacy or after successful long-term treatment, although the European Headache Federation has released some consensus-based guidelines [63].

6.2. *Tolerability and safety*

The tolerability and safety profiles of all four monoclonals are excellent and close to those of placebo. Erenumab tends to induce or worsen constipation, which is less frequently reported for the anti-CGRP mAbs. Since CGRP is abundant in the gastro-intestinal system [64], blocking its receptor might induce symptoms not produced by blocking CGRP, which still allows other ligands to act on the receptor. Galcanezumab is possibly associated with more injection site reactions, which was recently confirmed in a meta-analysis of the pivotal RCTs [65].

Since CGRP can act as a vasodilatory safeguard during cardiac (or cerebral) ischemia, neutralizing its effects by the mAbs could in theory worsen such events [66]. With follow-up now exceeding three years for erenumab, serious treatment-related vascular adverse events have not been reported [54,55]. This may be biased, however, by the fact that patients with recent cardio- or cerebrovascular events were excluded from the CGRP/rec mAb trials. A single administration of 140 mg erenumab in patients with stable angina did not aggravate exercise-induced angina or ST-segment depression [67]. This study, however, has been criticized because it included few women in whom, contrary to men, the distal coronary artery bed, the most sensitive to CGRP, is chiefly involved and because of the timing of erenumab's administration. Further long-term and real-world studies are thus needed to be definitively reassured [68].

Because of their lack of penetration through an intact blood-brain barrier [69], CGRP/rec mAbs are unlikely to cause central nervous system adverse effects. As mentioned before, however, the blood-brain barrier is lacking in some hypothalamic areas and the pituitary gland where the antibodies might interfere with CGRP effects [20]. Whether this may have clinical consequences over time remains to be studied.

If the action of CGRP/rec mAbs is restricted to the peripheral nervous system, it can be assumed that they have no effect on migraine aura, as confirmed by our real-life experience. By the same token, they probably have no effect on the cycling central dysfunctions that characterize the migraine brain interictally [11,14,15] and/or pre-ictally [10], illustrating that they are merely a symptomatic therapy with no modifying effect on the fundamental pathogenesis of migraine. It remains to be seen if the persistence of these

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central abnormalities may have clinical consequences on the long term. That some of our patients report the occurrence of ''phantom'' attacks with several migrainous features but without headache, despite an overall marked clinical improvement, may be due to the fact that the CGRP/rec mAbs act on the final common pathway of migraine pathogenesis at the ''funnel's narrow exit'' (see above Fig. 4), leaving central abnormalities unchanged.

According to animal experiments, CGRP, which abounds in motor neurons and periosteal sensory afferents, is involved in muscle endplate trophicity [70] and load-induced bone formation [71]. In theory, long-term blocking of CGRP or its receptor could thus interfere with these functions.

Finally, until studies in young patients are available, CGRP/rec mAbs are not yet recommended in children and adolescent migraineurs or should be used with caution in selected cases [72]. Until large prospective pregnancy registries have established their innocuity, CGRP/rec mAbs should be avoided during pregnancy. They can indeed penetrate the placenta where CGRP is a major vasodilator important for utero-placental blood flow and feto-placental development [4].

6.3. *The efficacy/adverse event ratio*

The precise positioning of CGRP/rec mAbs in the preventive anti-migraine armamentarium remains to determined and is (or has been) of concern for regulatory and reimbursement authorities in various countries. As already mentioned, no comparative trials with classical preventive drugs have been performed to date and thus one can only rely on comparisons of efficacy and tolerability results published separately for the two drug categories. The effect size of CGRP/rec mAbs is not clearly superior to that of topiramate, one of the most effective classical preventives. For instance, for topiramate 100 mg/d the NNT for the 50% responder rate in EM is 4 (therapeutic gain: 23.5%) [73] and depending on the trial, 4 or 13 in CM. Corresponding NNTs for the CGRP/rec mAbs vary between 4 and 5 in EM, between 4 and 8 in CM. The latter values in CM might indicate that the CGRP/rec mAbs perform better than onabotulinumtoxinA for which the corresponding NNT is 9 [74].

When CGRP/rec mAbs are compared with the other most effective preventives, their overwhelming advantage is the efficacy/adverse event ratio. While treatment-related adverse event rates for the CGRP/rec mAbs are at the placebo-level and exceptionally lead to treatment interruption, antidepressants, anticonvulsants and beta-blockers have frequent adverse effects leading, together with lack of efficacy, to their discontinuation in 50% of CM patients after two months of use [2]. This is reflected in number-needed-to-harm (NNH) figures as low as 13 for topiramate, as compared to 1000 for erenumab 70 mg. The NNH/NNT ratio reflecting the likelihood of being helped and not harmed is therefore almost 50 times greater for erenumab 70 mg than for topiramate 100 mg in CM [74].

It has been argued that non-drug therapies for migraine prevention might have an efficacy/tolerability profile comparable to that of the CGRP/rec mAbs. This was postulated for external trigeminal nerve stimulation [75] and acceptance and commitment therapy [76]. Trial evidence for the former, however, is based on a rather small number of patients with low frequency EM and a short follow-up [77], while the latter was assessed in an open pilot-study of 40 patients with high frequency EM. By contrast, the CGRP/rec mAbs are amongst the pharmacological classes used for migraine prevention the one that has been proven effective in the collectively largest RCTs ever conducted (over 5000 patients), including long durations of treatment (up to 5 years) and the most disabled patients.

6.4. *Cost effectiveness*

The present high pricing of CGRP/rec mAbs, their incomplete effectiveness and the assumption that less expensive and equally well-tolerated treatment alternatives might be as effective underscore the need for pharmaco-economic analyses. Three such studies have been published for erenumab. Two US studies performed a cost-effectiveness analysis of erenumab for the prevention of episodic and chronic migraine in patients with prior preventive treatment failure versus no preventive treatment or onabotulinumtoxinA. The estimated value-based price estimates at willingness-to-pay thresholds of $100,000–$200,000 for erenumab compared to supportive care ranged from $14,238–$23,998, and from $12,151–18,589 with onabotulinumtoxinA as a comparator including the placebo effect and excluding work productivity [78]. In the second study [79], the authors concluded that erenumab is a cost-effective therapy for the prevention of chronic migraine versus onabotulinumtoxinA or no preventive treatment, but is less likely to be cost-effective for episodic migraine, unless loss of productivity costs are considered. The pharmaco-economic study performed in Greece [80] found that incremental cost-effectiveness ratios for the treatment of CM with erenumab versus onabotulinumtoxinA were €218,870 (indirect costs included) per quality-adjusted life year gained and €620 per migraine avoided. For the erenumab incremental cost-effectiveness ratios to fall below the cost-effectiveness threshold equal to three times the local gross domestic product per capita (€49,000), the erenumab price would have to be no more than €192 (societal perspective), which is substantially lower than the present prices in most countries.

Taking together these first pharmaco-economic analyses suggest that erenumab is cost-effective for CM compared to no treatment or onabotulinumtoxinA, but likely not for EM unless attack frequency is high and indirect costs are considered. Its cost-effectiveness profile would obviously benefit from a lower price. Although the economic value of the anti-CGRP mAbs is likely comparable, further pharmaco-economic studies are clearly worthwhile.

Disclosure of interest

J.S. has participated in advisory boards of and received speaker's honoraria from Teva and Novartis. All authors have been involved in clinical trials with erenumab, fremanezumab and galcanezumab.

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