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COMMENTARY

Hellenic Headache Society Recommendations for the Use of Monoclonal Antibodies Targeting the Calcitonin Gene-Related Peptide Pathway for the Prevention of Migraine and Cluster Headache—2023 Update

D. D. Mitsikostas[1] · A. Alexoudi[2] · C. Arvaniti[3] · E. Giannouli[4] · E. Kouremenos[5] · T. S. Constantinidis[6] · N. Fakas[7] · C. Deligianni[8] · T. Karapanayiotides[9] · E. Dardiotis[10] · S. Gatzonis[2] · S. Konitsiotis[11] · G. Tsivgoulis[3] · Hellenic Headache Society

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Abstract

The confirmed involvement of the neuropeptide calcitonin gene-related peptide (CGRP) in the pathophysiology of migraine has led to the development of treatments, which for the first time are specific to migraine and mechanism based, in contrast to repurposed traditional prophylactic anti-migraine medications. Thus, in the last 5 years, the European Medicines Agency (EMA) approved four monoclonal antibodies that target either the CGRP ligand (eptinezumab, fremanezumab, and galcanezumab) or the CGRP receptor (erenumab). These anti-CGRP therapies are indicated for use in people with migraine who have more than 4 migraine days per month. In this consensus article, the Hellenic Headache Society highlights the indications and treatment protocols of these novel anti-migraine therapies, aiming to assist Greek neurologists in the optimal management of people with migraine. The recommendations are based on data from phase 3 randomized-controlled clinical trials, the recent European Headache Federation (EHF) recommendations, a consensus article under the auspices of both the EHF and the European Academy of Neurology (EAN), recent real-world evidence studies, and the authors' acquired clinical experience.

Keywords Guideline · Migraine · Prophylactic and/or preventative treatment · CGRP · Anti-CGRP monoclonal antibodies · Erenumab · Fremanezumab · Galcanezumab · Eptinezumab

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✉ D. D. Mitsikostas
dmitsikostas@uoa.gr

1 First Department of Neurology, Medical School, Aeginition Hospital, National and Kapodistrian University of Athens, 74 V. Sofia's Avenue, 11528 Athens, Greece

2 First Department of Neurosurgery, Medical School, Evangelismos Hospital, National and Kapodistrian University of Athens, Athens, Greece

3 Second Department of Neurology, Medical School, "Attikon" University Hospital, National and Kapodistrian University of Athens, Athens, Greece

4 Headache Clinic, Athens Medical Center, Athens, Greece

5 Neurology Department, 251 General Hospital of Air Forces, Athens, Greece

6 Neurology Clinic, Corinth, Greece

7 Neurology Department, 401 General Military Hospital, Athens, Greece

8 Neurology Department, Athens Naval Hospital, Athens, Greece

9 Second Department of Neurology, Medical School, AHEPA Hospital, Aristotelion University of Thessaloniki, Thessaloniki, Greece

10 Neurology Department, Medical School, University Hospital of Larissa, University of Thessaly, Larissa, Greece

11 Neurology Department, Medical School, University Hospital of Ioannina, University of Ioannina, Ioannina, Greece

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Introduction

The calcitonin gene-related peptide (CGRP) belongs to a family of peptides that include adrenomedullin, amylin, and calcitonin with a variety of biological functions in the body and central nervous system (CNS) [1]. CGRP is the strongest vasodilator peptide on the human body, but in addition to the smooth muscle fibers of the vessel wall, CGRP mRNA is also detected in the endings of the C and Aδ sensory nerve fibers of the trigeminovascular system [2]. Extensive studies from different laboratories around the world, both in animals and humans, demonstrated the involvement of CGRP in the pathophysiology of migraine [3]. Increased levels of CGRP alone but not any other neuropeptides, e.g., the neuropeptide Y and substance P, were initially documented during a migraine attack in humans [4]. Subsequently, animal studies showed that the symptomatic anti-migraine drugs triptans, which are selective 5-HT1B/1D receptor agonists, are associated with inhibition of CGRP [5, 6]. Later, it was observed that intravenous administration of CGRP to migraineurs induces migraine without aura, which relieves with sumatriptan [7]. In addition, inhibitors of the CGRP receptor relieve migraine [8]. These findings led to the development of monoclonal antibodies against CGRP, which after a large clinical program of studies have demonstrated good efficacy and excellent tolerance, when administered to migraineurs for the prophylaxis of episodic and chronic migraine [9, 10]. Three biological agents (monoclonal antibodies) against the ligand CGRP (eptinezumab, fremanezumab, and galcanezumab) and one against the CGRP receptor (erenumab) have already been approved by the European Medicines Agency (EMA) for use in the prophylactic treatment of migraine in the European Union [11–14]. Three of them are currently marketed in Greece (erenumab, fremanezumab, and galcanezumab), licensed for people with more than 4 monthly days with migraine. All three biologic agents are 100% reimbursed, but only through an Electronic Prior Authorization System (ePAS) and only if at least three traditional migraine medications have failed or are contraindicated and only if there is headache diary documentation of more than 8 migraine days/month. Hundreds of people with migraine have already started prophylactic treatment with anti-CGRP biological agents through ePAS, as well as through participation in phase 3 randomized-controlled clinical trials (RCTs). Many people also have private insurance that covers the cost of treatment, while others cover the purchase of the drug at their own expenses. The Hellenic Headache Society (HHS) has published a consensus statement proposing ways to use anti-CGRP biological agents [15] based on the guidelines of the European Headache Federation (EHF) [16]. Following the acquisition of relevant clinical experience and the publication of real-world observational studies, EHF has recently updated the 2019 recommendations [17]. For the same reasons, the HHS also decided to update the 2019 guidelines for the use of anti-CGRP monoclonal antibodies (anti-CGRP mAbs), as it was stated in the original text. The consensus article under the auspices of the EHF and the European Academy of Neurology (EAN) [18], the recent guidelines of EHF for the use of anti-CGRP mAbs [17], the real-world studies of anti-CGRP mAbs [19], and the personal experience of the panelists were the basic elements for the update aiming at improving decision-making in daily clinical practice in Greece.

Monoclonal Antibodies Targeting the CGRP Pathway for the Prophylactic Treatment of Episodic and Chronic Migraine

Biological agents or monoclonal antibodies (mAbs) are homogeneous populations of immunoglobulins derived from a single plasmacyte with a predetermined specificity towards an antigenic epitope and potential for in vitro worm production [20]. Due to their high molecular weight, they do not to cross the blood–brain barrier and their site of action is peripheral, within the trigeminal-vascular system. The half-life of all mAbs is long, and all of them that are currently marketed in Greece (with the exception of eptinezumab) are administered subcutaneously once a month (or once every 3 months for the case of 625 mg of fremanezumab) [9, 10]. In summary, the key characteristics of the four EMA-approved biological agents for migraine prophylaxis are presented in Table 1. The phase 3 RCTs documenting the efficacy of each anti-CGRP mAb are summarized in Table 2 for episodic migraine and Table 3 for chronic migraine. These studies showed that the efficacy of anti-CGRP mAbs in the prophylaxis of episodic and chronic migraine is superior to placebo. There is only one randomized phase 3B RCT that compared erenumab (70 or 140 mg/month) with topiramate (50 to 100 mg/day), a traditional anti-migraine synthetic drug, in the prophylaxis of episodic migraine, the HERMES study [34]. The primary endpoint was the treatment discontinuation due to adverse events, and the predetermined secondary endpoint was the proportion of patients with a 50% reduction in migraine days/month. This study was carried out in Germany exclusively. In the intention to treat analysis, it was found that 10.6% of the participants treated with erenumab discontinued treatment due to AEs compared to 38.9% in the topiramate group (odds ratio, 0.19; 95% confidence intervals: 0.13–0.27; $p < 0.001$). In addition, more participants achieved a $\geq 50\%$ reduction in monthly migraine days with erenumab treatment than with topiramate

Table 1 Basic characteristics of monoclonal antibodies targeting the CGRP pathway that are indicated for migraine prophylaxis and are marketed in Greece

	Erenumab AMG334	Eptinezumab ALD403	Fremanezumab TEV-48125	Galcanezumab LY2951742
Trade name	Aimovig™	Vyepti™	Ajovy™	Emgality™
Pharmaceutical company	Amgen/Novartis	Lundbeck	Teva	Eli Lilly & Co
Molecular composition	Human IgG_2	Humanized IgG_1	Humanized IgG_2	Humanized IgG_4
Target	CGRP receptor	Ligand CGRP	Ligand CGRP	Ligand CGRP
Administration	Subcutaneously	Intravenous	Subcutaneously	Subcutaneously
Delivery mode	Pre-filled pen containing 70 or 140 mg	Vial containing 100 mg	Pre-filled syringe containing 225 mg	Pre-filled pen containing 120 mg
Frequency of administration and dose	70 or 140 mg monthly	100 mg monthly or 300 mg quarterly	225 mg monthly or 675 mg quarterly	120 mg monthly (initial dose 240 mg)
Approval EMA	August 8, 2018	February 15, 2022	April 17, 2019	February 14, 2019
Marketed in Greece	February 2019	Expected commercialization within 2023	July 2020	June 2021
100% reimbursement after approval	February 2022	Not reimbursed	July 2021	November 2022

(55.4% vs. 31.2%, odds ratio 2.76, 95% confidence intervals: 2.06–3.71, $p < 0.001$). No relevant safety concerns of erenumab were observed [34]. In indirect comparisons, the anti-CGRP mAbs had similar efficacy to propranolol and topiramate in episodic migraine and to topiramate and onabotulinumtoxinA in the prophylaxis of chronic migraine, but the risk–benefit ratio (e.g., the likelihood to help versus to harm) was in favor of anti-CGRP mAbs [35], making these agents protagonists in migraine therapeutics.

The most common adverse events (AEs) in the phase 3 RCTs of anti-CGRP mAbs in migraine prevention were mostly mild to moderate in severity with similar incidence rates between the study drug group and the placebo group. Adverse events leading to treatment discontinuation were reported in very low rates (1–4%) and were mainly related to constipation and fatigue intolerance, but these rates were similar in the placebo group. Adverse events with a frequency of > 2% were upper respiratory tract infections, nausea, sinusitis, pharyngitis, urinary tract infection, arthralgias, muscle spasms, and dizziness. There was no hepatotoxicity, an increase in blood pressure, or an increased risk for any heart disease or vascular event. It should also be emphasized that the anti-CGRP mAbs used in migraine do not target the immune system, and in this point, they differ considerably from the biological therapies used in other diseases such as multiple sclerosis, cancer, or systemic inflammatory diseases [20]. Data from the RCTs with anti-CGRP mAbs in migraine have shown the development of neutralizing antibodies in a very small percentage of cases, from 0 to 3.1%. Thus, it is not considered necessary to measure neutralizing antibodies in daily clinical practice [21–33]. Also, routine measurement of neutralizing antibodies is not recommended by the EHF, the EAN, and any other scientific society.

The prospective, observational, real-world studies that have since been published (Table 4) add a lot of important information mainly on the safety of anti-CGRP mAbs, given that they extend over a period of more than 6 months [36–41]. Overall, real-world studies showed significant efficacy in treating episodic and chronic migraine with response rates comparable to the numbers reported in phase 3 RCTs, or even higher. However, it should be noted that in some studies, the percentages of AEs were much higher than those reported in phase 3 RCTs [36, 42]. Arterial hypertension and constipation were recorded as expected AEs of erenumab and are now listed in the SPC of this agent [36, 43].

Recommendations for the Use of Anti-CGRP mAbs in Episodic and Chronic Migraine

Recommendations are categorized into strong and weak according to the documentation and experience of the authors. Documentation of a recommendation is considered good when it is based on at least 2, placebo-controlled RCTs. Moderate documentation corresponds to data from only one placebo-controlled RCT. Poor documentation is based on data from observational studies only.

1. We recommend to carefully educate people with migraine on the correct use of symptomatic medications and the avoidance of known triggers, before suggesting any prophylactic pharmacological treatment [44]. (*Strong recommendation, poor documentation*)
2. We recommend the anti-CGRP mAbs as first-line pharmacological treatment for the prevention of migraine in people older than18 years with 4 or more days with migraine/month, along with the traditional

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Table 2 Phase 3 RCTs for prevention of episodic migraine with anti-CGRP monoclonal antibodies

Trial	Anti-CGRP monoclonal antibody	Dose (mg)	# participants in the active arm	# participants in the placebo arm	Treatment duration (weeks)	% participants with > 50% reduction in the active arm	% participants with > 50% reduction in the placebo arm	% drop-outs due to AE in the active arm	% drop-outs due to AE in the placebo arm
STRIVE [21]	Erenumab	70	317	319	24	43.3	26.6	2.2	2.5
		140	319			50.0		2.2	
ARISE [22]	Erenumab	70	286	291	12	39.7	29.5	1.8	0.3
EMPOWER [23]	Erenumab	70	338	338	12	55.3	44.8	0	0.6
		140	224			63.9		0	
LIBERTY[24]	Erenumab	140	119	124	12	30	14	0	1
PROMISE-1 [25]	Eptinezumab	30	219	222	12	50.2	37.4	5.5	2.7
		100	223			49.8		2.7	
		300	224			56.3		2.2	
HALO EM [26]	Fremanezumab	225	287	290	12	47.7	27.9	1.7	1.7
		675	288			44.4		1.7	
NCT03303092 [27]	Fremanezumab	225	121	117	12	41.3	11.2	0.8	0.9
		675	119			45.3		0.4	
EVOLVE-1 [28]	Galganezumab	120	213	433	24	62.3	38.6	< 5%	< 5%
		240	212			60.9		< 5%	
EVOLVE-2 [29]	Galganezumab	120	231	461	24	55.6	33.4	2.2	1.7
		240	223			52.6		4.0	

Table 3 Phase 3 RCTs for prevention of chronic migraine with anti-CGRP monoclonal antibodies

Trial	Anti-CGRP monoclonal antibody	Dose (mg)	# participants in the active arm	# participants in the placebo arm	Treatment duration (weeks)	% participants with > 50% reduction in the active arm	% participants with > 50% reduction in the placebo arm	% drop-outs due to AE in the active arm	% drop-outs due to AE in the placebo arm
Tepper et al. 2017 [30]	Erenumab	70	191	286	12	40.0	23.0	0	< 1
		140	190			41.0		1.0	
PROMISE-2 [31]	Eptinezumab	100	356	366	12	57.6	39.3	< 1	< 1
		300	350			61.4		2.3	
HALO-CM [32]	Fremanezumab	225	379	375	12	41	18	2	2
		675	376			38		1	
REGAIN [33]	Galcanezumab	120	278	558	12	27.6	15.4	< 1	1
		240	277			27.5		1	

anti-migraine therapies (e.g., anti-hypertensives, anti-depressants, anti-epileptics, anti-vertigo medicines, and onabotulinumtoxinA for the case of chronic migraine only). The choice of the best optimum treatment depends on the comorbidity and the preferences of the patient. Therefore, the therapeutic decision is recommended to be individualized from the outset and not be stratified. This recommendation is presumed from the data presented in Tables 2 and 3, the head-to-head comparative study of erenumab and topiramate [34], the indirect comparative study of anti-CGRP mAbs with traditional anti-migraine pharmacological treatments [35], and the data from the real-world studies (Table 4). Additionally, anti-CGRP mAbs have also been proved to be financially beneficial in a cost–benefit analysis study adapted to the Greek economy [45]. Notably, there is good documentation for the use of anti-CGRP biological agents in people with migraine who are older than 65 years [46–48]. (*Strong recommendation, good documentation*)

3. We recommend the headache diary as the primary instrument for assessing treatment outcomes. Alternatively, other scales can be used (e.g., MIDAS or HIT-6), which are also standardized in Greek individuals [49, 50]. The headache diary was the tool for monitoring the primary endpoints in all phase 3 RCTs while the MIDAS and HIT-6 scales were used for secondary outcomes (Tables 2 and 3). (*Strong recommendation, good documentation*)
4. We recommend treatment with anti-CGRP mAbs for more than 3 months initially. If there is no greater than 50% reduction in headache days/month compared to the pre-treatment period, and/or the person under treatment remains unsatisfied, we recommend discontinuing treatment and switching to another preventative medication. There are studies indicating that a significant number of people with migraine respond to treatment after 3 months of treatment [36; 51–54] like in the case of onabotulinumtoxinA [55]. Thus, the first evaluation is recommended to be done at least after 3 months of treatment. (*Strong recommendation, moderate documentation*)
5. We recommend prophylactic treatment with anti-CGRP mAbs in people with migraine and overuse of symptomatic anti-migraine medications, because post hoc analyses of the phase 3 studies for all four anti-CGRP mAbs showed significant efficacy over placebo in this group of people [56–60]. However, there are no placebo-controlled RCTs with anti-CGRP mAbs in people with migraine and medication overuse exclusively. (*Strong recommendation, poor documentation*)
6. When treatment with anti-CGRP mAbs is successful in the first assessment (reduction ≥ 50% of headache

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Table 4 Prospective real-world observational studies with anti-CGRP monoclonal antibodies for the prophylaxis of migraine

Trial	Anti-CGRO monoclonal antibody	Country	Principal inclusion criterion	# participants	Treatment duration (weeks)	% participants with > 50% reduction	% drop-outs due to AE	% participants with any AE	Most common AE (%)
Lambru et al. (2020) [36]	Erenumab	UK	Resistant chronic migraine	162	24	38	12	48	Constipation (20), flu symptoms (15)
Andreou et al. (2022) [37]	Erenumab	UK	Resistant chronic migraine	164	96	16	13	4	Constipation (4)
Torres-Ferrus et al. (2021) [38]	Erenumab (70%) Galcanezumab (30%)	Spain	Resistant chronic and episodic migraine	155	12	51.6	16.1	29	Constipation (20), fatigue (7), increase BP (5)
Cullum et al. (2022) [39]	Erenumab	Denmark	Migraineurs under treatment with erenumab or fremanezumab	300	52	64.2	13.7	73.3	Constipation (41.3), nausea (7.3), fatigue (6.6)
Barbanti et al. (2022) [40]	Fremanezumab	Italy	Migraineurs under treatment with fremanezumab	67	12	76.5	0	5.7	Erythema at the injection site
Vernierietal et al. (2021) [41]	Galcanezumab	Italy	Migraineurs under treatment with galcanezumab	163	24	EM: 76.5, CM: 63.5	6.1	2	Constipation (2), erythema at the injection site (2)

days/month and/or treated person satisfied), we recommend that it should be continued for at least 12 additional months, for a second assessment. Pause of treatment may be suggested to evaluate potential migraine relapse, lasting 1 to 2 months. In case of a relapse, re-administration of the initial treatment is recommended. There is poor documentation for this recommendation, which is based on two observational studies that found a clear relapse of migraines to discontinuation of treatment before the completion of 1 year [61, 62]. (*Strong recommendation, poor documentation*)

7. We recommend avoiding anti-CGRP mAbs in pregnant or lactating women because there is no relevant safety documentation. We recommend caution and individual decision to administer an anti-CGRP mAb to individuals with vascular disease or to individuals with risk factors for vascular disease, or to individuals with Raynaud's phenomenon. In addition, particular caution is advised in the use of erenumab in people with migraine and a history of severe constipation [36] and/or arterial hypertension [63]. (*Strong recommendation, moderate documentation*)
8. When the response to an anti-CGRP mAb is inadequate, administration of another anti-CGRP mAb may be attempted, especially when the target of the new treatment is different (e.g., CGRP ligand or CGRP receptor). There is poor scientific evidence for this recommendation with two observational studies in which 30% of patients who did not respond to an anti-CGRP mAb had a clear improvement after initiation of treatment with another anti-CGRP mAb [64, 65]. Moreover, this recommendation is in line with the framework of daily medical practice. (*Weak recommendation, poor documentation*)
9. There is insufficient evidence to make recommendations on a possible combination of anti-CGRP biological agents with other prophylactic anti-migraine pharmacological treatments. In clinical practice, this is certainly the case, and in the case of chronic migraine, there is a recent study of coadministration of onabotulinumtoxinA with an anti-CGRP mAb providing favorable results [66]. (*Weak recommendation, poor documentation*)
10. A neurologist with appropriate training or dedicated headache centers should guide initiation, monitoring, and discontinuation of anti-CGRP mAb therapy, because knowledge is required not only of pain neurotransmission but also of the broader CNS neurovascular environment, since CGRP has a strong vasodilator effect [1]. Thus, only a neurologist or other physicians with special training may effectively manage the use of anti-CGRP mAbs in people with migraine and other potential comorbidities, in the event that the number of neurologists is sufficient to treat migraine patients. (*Weak recommendation, undocumented*)

These recommendations do not cover all the questions arising from the use of anti-CGRP mAbs in clinical practice. The specific clinical features of migraines or other biomarkers predicting the efficacy for an anti-CGRP mAb have not been studied. The same applies to the class of drugs against CGRP versus the other classes of anti-migraine drugs. Erenumab and fremanezumab have two different dosing regimens, which have been accepted as being of equal efficacy and safety. Therefore, no recommendation has been issued with regard to the use of any dose at the beginning of treatment. In two phase 3 RCTs, erenumab 140 mg had better efficacy compared to the 70 mg dose [21, 23], but the difference had marginal statistical significance. Dose increase from 70 to 140 mg did not affect the 50% migraine attack reduction efficacy criterion in an observational study, but more patients achieved the 30% reduction in migraine attacks/month with the higher erenumab dose [36].

Anti-CGRP Biological Agents in Cluster Headache

Based on clinical data claiming that during a spontaneous cluster headache (CH) attack, external jugular vein blood levels of CGRP are raised and reduced after successful treatment with sumatriptan or oxygen [67] and that infusion of CGRP may trigger a CH attack in the vast majority of people with CH within a bout [68], clinical studies with anti-CGRP mAbs as prophylactic treatment of CH were designed. Galcanezumab was tested in a placebo-controlled RCT in 106 individuals with episodic CH [69]. Although the study ended prematurely due to a low rate of participant enrolment, a significant reduction in the weekly frequency of CH attacks was observed after administration of only one dose of 300 mg galcanezumab (minus 8.7 attacks), compared to placebo (minus 5.2 attacks) for a total of 3 weeks. The adverse events of galcanezumab were similar to placebo, except from the pain at the site of administration that was reported by 8% of participants receiving galcanezumab. Another multicenter, placebo-controlled RCT of galcanezumab (300 mg) in 237 participants with chronic CH did not reach the primary endpoint (significant reduction in weekly frequency of CH attacks relative to baseline frequency) [70]. Fremanezumab (a single intravenous administration of 225–900 mg) was tested in two multicenter placebo-controlled RCTs, one in chronic CH (https://clinicaltrials.gov/ct2/show/NCT02945046) and the other in episodic CH (https://clinicaltrials.gov/ct2/show/NCT02964338), which unfortunately ended prematurely, because the planned interim analysis showed futile results. These studies did not provide any new safety

Table 5 Recommendations for the use of anti-CGRP monoclonal antibodies in the prophylaxis of migraine

Recommendation	Strength	Documentation	References
Before suggesting any prophylactic pharmacological treatment, detailed education on the proper use of symptomatic medications and avoidance of known migraine triggers is recommended	Strong	Poor	[44]
The anti-CGRP monoclonal antibodies erenumab, fremanezumab, galcanezumab, and eptinezumab are first-line prophylactic treatments in people with migraine aged > 18 years with > 4 migraine days/month	Strong	Good	[21–35] [45–48]
For treatment follow-up, it is necessary for the patient to keep a headache diary and alternatively the MIDAS and/or HIT-6 questionnaires	Strong	Good	[21–33, 49, 50]
Treatment with anti-CGRP mAbs is recommended for at least 3 months initially, until the first efficacy assessment	Strong	Moderate	[36]; [51–55]
After the first assessment and if treatment with an anti-CGRP mAb is successful (> 50% reduction in headache days/month), we recommend continuation of the treatment for additional 12 months at least; the treating physician will decide whether pause of treatment or not is required to determine potential recurrence of migraine after the second assessment	Strong	Poor	[61]; [62]
In people with migraine and medication, overuse preventive treatment with an anti-CGRP mAb is recommended	Strong	Poor	[56–60]
Avoidance of anti-CGRP mAbs in pregnant and lactating women is recommended. Special caution is required when anti-CGRP mAbs are administered to people with vascular predisposing factors and Raynaud's phenomenon. Special extra care is required for erenumab when it is administered to people with constipation and arterial hypertension	Strong	Poor (moderate for the case of erenumab and hypertension)	[37], [63]
When response to one anti-CGRP mAb is inadequate, administration of another anti-CGRP mAb may be attempted	Weak	Poor	[64]; [65]
Combination of anti-CGRP mAb with other prophylactic anti-migraine medications can be given in refractory migraine, or in cases of comorbidities	Weak	Poor	[66]
The initiation, monitoring, and discontinuation of treatment with an anti-CGRP mAb should be guided by a neurologist	Weak	No documentation	

data. Ongoing trials are testing the efficacy of eptinezumab in episodic CH and erenumab in chronic CH (NCT04688775 and NCT04970355, respectively). The existing evidence, therefore, may support for efficacy of galcanezumab as a prophylactic treatment for episodic CH [71], licensed by the Food and Drug Administration (FDA), but not by the EMA. Its administration could, however, be tested on refractory cases of CH at doses of 240–360 mg/month, as several observational studies substantiate [72–74].

Emerging Treatments for Migraine

In addition to the biological agents targeted at CGRP pathway, there are also synthetic molecules, administered orally, that inhibit the binding of CGRP to its receptor. These medications mostly do not cross the blood–brain barrier and do not cause vasoconstriction and form another anti-migraine drug class, the gepants [75]. The likelihood of headache from gepant withdrawal is theoretically lower because these medications compete with the CGRP receptor, unlike other anti-migraine drugs that activate receptor systems (e.g., triptans that are selective agonists for the 5-HT1B and 5-HT1D receptors) [76]. Therefore, the gepants are symptomatic anti-migraine medications with possible prophylactic anti-migraine action. Indeed, rimegepant has demonstrated in phase 3 RCT efficacy in both symptomatic [77] and prophylactic treatment for episodic migraine [78] and has been approved by the FDA and EMA for both uses at a dose of 75 mg (for prophylaxis on every other day administration 75 mg and for symptomatic treatment 75 mg one-off). A second synthetic anti-CGRP molecule of the gepant class, atogepant, is under evaluation by the EMA for use exclusively in the preventive treatment of episodic and chronic migraine [79] (https://clinicaltrials.gov/ct2/results?term=NCT03855137&draw=2&rank=1#rowId0).

Conclusions

A number of innovative therapies targeting CGRP or its receptor have recently become available in Europe. Prescribing through electronic pre-approval by the authorities with full reimbursement, three anti-CGRP biological agents, erenumab, fremanezumab, and galcanezumab, are currently marketed in Greece and eptinezumab is expected soon. As with any new treatment, integration into clinical practice is essential to provide the best possible care to

those who need it, taking into account the safety, tolerance, and effectiveness of the novel treatments [80, 81]. The aforementioned recommendations (Table 5) express the detailed opinion of the Hellenic Headache Society, after evaluating the recent available data. Needless to say that they will have to be re-evaluated in the near future, especially when newer data emerge that may challenge the present recommendations. Other anti-CGRP prophylactic treatments for migraine are imminent. Gepant is a novel anti-migraine drug-class consisting of oral, synthetic drugs that antagonize the CGRP receptor. Rimegepant and atogepant are representatives of gepants. Rimegepant is the only pharmacological agent so far with an indication for both symptomatic and prophylactic treatments of migraine approved by both FDA and EMA, while atogepant has an indication for the prophylaxis of migraine by FDA and is under evaluation by the EMA. Currently, therefore, for the pharmacological prophylaxis of episodic migraine (monthly days with migraine < 15), the treating physician has to choose a medication for episodic migraine from 5 drug classes (anti-CGRP mAbs, anti-depressants, anti-epileptics, anti-hypertensives, and Ca-blockers). For the prophylaxis of chronic migraine (monthly days with migraine ≥ 15), the list of proposed evidence-based treatments includes only 5 medicines (3 anti-CGRP mAbs, onabotulinumtoxinA, and topiramate). It should be noted however that the documentation of the efficacy and the safety and tolerance of topiramate in the prevention of chronic migraine clearly fall short of the anti-CGRP mAbs and onabotulinumtoxinA, moving topiramate at the second line of treatment [34, 80–82]. The same applies to medication for episodic migraine prophylaxis. Traditional repurposed anti-migraine drugs lack the documentation of anti-CGRP mAbs, and only topiramate shares a comparable clinical program to test efficacy in the prevention of episodic migraine, which unfortunately suffer from low adherence and tolerance. Nevertheless, the list of preventive anti-migraine medications will soon be expanded in Greece with an anti-CGRP mAb, eptinezumab, and two gepants. From all these treatments, one should be selected for each individual with migraine. The decision process should be individualized from the outset, depending on the comorbidity, previous therapeutic efforts, and patient's personal preferences and lifestyle choices. Educating the patient to avoid known migraine triggers and to use symptomatic medications properly is essential, while the possibility of using non-pharmacological therapies should always be discussed [80, 81]. Often the patient expects migraine elimination or at other times considers the migraine incurable, so he or she should be informed about the goals and effectiveness of the proposed treatment in detail. Whatever the consensual treatment choice by the doctor-patient dyad, re-evaluation should include, in addition to efficacy and adverse effects, compliance with medication adherence, and agreed-upon behavioral changes by the patient.

Author Contribution DDM led the consensus process and drafted the manuscript. All other authors participated in the development of the expert consensus statements, and all revised the manuscript and approved the statements for content.

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Code Availability Not applicable.

Declarations

Ethics Approval Approval was not sought from any ethics committee because no data from patients were analyzed, while only a review of the relevant bibliography was performed.

Consent to Participate Not applicable.

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