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CGRP Monoclonal Antibodies for the Preventative Treatment of Migraine

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Abstract

Purpose of Review CGRP is a key neuropeptide in migraine pathophysiology. The blockade of the CGRP pathway at the side of the CGRP receptor of the CGRP peptide leads to the interruption of trigeminal nerve system-mediated headache syndromes such as migraine. Monoclonal antibodies (mAbs) targeting the CGRP pathway have been developed and are currently under investigation for episodic (EM) and chronic migraine (CM) prevention. Here, we report data from these clinical trials.

Recent Findings Placebo-controlled, randomized double-blind phase studies of CGRP mAbs in episodic and chronic migraine have shown that the specific blockade of the peptide or the CGRP receptor are both powerful mechanisms to reduce migraine frequency. Along with the reduction of acute migraine-specific medication intake, early onset of efficacy of mAbs has been demonstrated. Most common adverse events are injection sider reactions. Depending on the mAb, the administration mode is a monthly or even less frequently s.c. or I.V. formulation.

Summary Phase II studies in EM and CM demonstrate that CGRP mAbs are effective anti-migraine preventatives with a beneficial adverse event profile. Further detailed results from larger phase III clinical trials are expected soon.

Keywords Chronic migraine · Episodic migraine · CGRP antibody · Migraine prevention · Antibody safety

Introduction

Monoclonal antibodies (mAbs) interfering in the calcitonin gene-related peptide (CGRP) signaling pathway are novel treatment options for the prevention of migraine. While most mAb clinical development programs for migraine are beyond phase III trial stage, data from trials for the prevention of cluster headache are not finished yet. Four mAbs, i.e., eptinezumab, erenumab, fremanezumab, and galcanezumab are currently under investigation in episodic (EM) and chronic migraine (CM) [1•], while only fremanezumab (NCT02945046, NCT02964338) and galcanezumab (NCT 02397473, NCT02438826) are studied in cluster headache prevention.

Eptinezumab, fremanezumab, and galcanezumab mAbs bind to the CGRP molecule, while erenumab specifically blocks the canonical CGRP receptor, which is expressed, e.g., on neurons and blood vessels [2]. CGRP is involved in vasodilation, but it seems not to alter vascular diameter under physiological conditions [3]. This molecule also serves as a neuropeptide in several tissues within the body. CGRP's role is understood in migraine pathophysiology but in other disorders linked to CGRP, e.g., irritable bowel syndrome or joint pain [2, 4]. Therefore, the use of CGPR antibodies in a large migraine population will also provide insight of the role of CGRP in the pathogenesis of other disorders. By nature, these CGRP monoclonal antibodies are peptides and therefore administered in a non-oral formulation. Hence, daily tablet intake will not be necessary for the patients on these preventatives in the future. The discussions with patients about their compliance or adherence will no longer be most relevant. With currently available migraine preventatives, adherence is lower than 30% after 6 months in chronic migraine patients [5]. Due to a long half-life time with a range of 21 days for erenumab to 45 days for fremanezumab, mAbs need to be administered once a month or even less frequently [2]. Once these substances are approved, real-world evidence will tell us more about the administration frequency. Of note, eptinezumab is developed in an intravenous formulation while erenumab,

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fremanezumab, and galcanezumab are administered subcutaneously. Among the mAbs, erenumab is the only fully human monoclonal antibody. Finally, mAbs are not metabolized in the liver, in contrast to small molecule CGRP receptor antagonists, which were mainly tested for acute migraine treatment.

Migraine patients are in search of effective preventative therapies with a fast onset of action with few adverse events, according to a survey in American and Brazilian migraine patients [6]. Interestingly, weight loss is the only accepted side effect of migraine prophylactic drugs. In contrast, depression, weight gain, and memory and energy loss are rejected to a large extent [7].

For chronic migraine, only botulinum toxin therapy is approved in the USA and topiramate and botulinum toxin in several European countries. Treatment need is highest in this population [8]. Fifty percent of CM patients who stop preventive therapy complain about insufficient efficacy and/or adverse events, which in turn lead to treatment termination [9].

In chronic migraine placebo-controlled randomized double-blind phase II/III studies with erenumab, fremanezumab and galcanezumab have finished the double-blind treatment phase. One phase III trial with eptinezumab (ALD403-CLIN-011) is ongoing. Since some of the data have not been presented in full paper yet, we will illustrate findings for the two subclasses (CGRP antagonist/CGRP receptor antagonist) based on the peer-reviewed publications. Of note, published trial results in abstract form (galcanezumab, fremanezumab, and eptinezumab) also show superiority of active substance over placebo for numerous endpoints but will not be discussed here. It is important to understand that primary endpoints are different between the following CM trials.

Chronic Migraine Phase II Trial Data

Fremanezumab (formerly TEV 4812; NCT02021773) reduced monthly headache hours (primary endpoint) in CM in treatment weeks 8–12 superior to placebo from baseline 157 h (900 mg), 159 h (675/225 mg), and 169 h (placebo) by 67.1 h (900 mg; $p = 0.0057$), 59.8 h (675/225 mg; $p = 0.0386$) vs. 37.5 h (placebo) [10••]. About 90 subjects per group with 13.9–13.1 severe headaches/4 weeks of moderate to severe intensity were studied. Headache days were also reduced by 6.1 (900 mg; $p = 0.004$) and 6.04 (675/225 mg; $p = 0.069$) with a difference to placebo (4.21-day reduction) of 2 days. Treatment failure to more than two preventatives was one of the important exclusion criteria in this trial. Medication overuse was allowed and patients could also be on one or two stable preventive medications in parallel to treatment in this study. Onabotulinumtoxin was not allowed a co-medication.

Pooled subgroup analysis from this and the episodic fremanezumab phase II trial (NCT02025556) shows that fremanezumab given as add-on therapy reduces the mean number migraine days from 14.6 per month by 4.12 ($n = 67$) while placebo ($n = 66$) leads to a 2.47-day reduction ($p < 0.05$) [11]. The 50% responder rate was also favorable for fremanezumab (40%) over placebo (24%) The majority of subjects in this analysis were on non-sufficient but stable doses of ß-blockers or topiramate. This is one of the few trials/analysis, which shows that adding a preventative to non-sufficient prophylactic medications provides additional benefit to the patient. While combining centrally acting propranolol to topiramate did not provide any additional efficacy [12], it seems that adding a targeted specific peripheral therapy (CGRP antagonist) to an unspecific centrally acting agent leads to additional benefit. Since this is only a promising subgroup analysis, larger placebo-controlled randomized double-blind clinical trials investigating the combination of CGRP mAbs with currently available preventatives should follow on order to provide further insight.

Monoclonal CGRP antibodies show early onset of action. In another post hoc analysis by Bigal et al., fremanezumab showed clear beneficial separation from placebo by day 7 (675/225-mg dose) for headache hours and also in treatment week 2 for moderate to severe headache days. This benefit is consistent over the entire trial period [13].

In a larger placebo-controlled randomized double-blind trial (NCT02066415) with 670 CM subjects, erenumab clearly demonstrated superiority for both tested doses (70/140 mg) over placebo [14••]. The population in this trial reflected typical CM cohorts in clinical practice, at an average mean age of 42 years, and females (80%). This population displayed an average of 18 monthly migraine days (MMD) with a use of ~ 9 triptan intake days during baseline. Fifty percent of subjects in this trial failed more than two preventative medications prior to this trial. Primary endpoint was the change of monthly migraine days from the baseline phase to the last 4 weeks of the 12-week double-blind treatment phase (weeks 8–12). The first s.c. injection of either dose of erenumab led to a reduction of 5 migraine days/month (week 1 to week 4) while placebo led to − 2.7 migraine days. At month three (weeks 8–12) erenumab had a significant advantage of 2.4 migraine days over placebo (− 6.6 MMD for erenumab; − 4.2 days for placebo; $p < 0.0001$ for both doses). Only 23% of the subjects with placebo but 40 and 41% with erenumab (70 and 140 mg; $p < 0.0001$ for both doses) had a 50% or greater reduction in MMD. The clear benefit of mAb treatment on migraine is supported by a reduction of − 3.5 (70 mg) and respectively − 4.1 (140 mg) specific migraine-specific medication days (placebo − 1.6; $p < 0.0001$ for both doses). Safety data will be discussed together with results from the EM trials.

Results from the phase III CM trial with galcanezumab (NCT02614261) are expected to be published in a peer review journal shortly. In the phase III fremanezumab CM trial, Silberstein and colleagues [15••], primarily analyzed moderate to severe headache days in 1130 chronic migraine subjects

(29). Subjects received either a single dose of 675 mg fremanezumab followed by placebo at weeks 4 and 8 (quarterly group) or 675 mg at baseline and 225 mg at weeks 4 and 8 (monthly group) or placebo at all three time points. Subjects reported an average of 13.2 (quarterly), 12.8 (monthly) and 13.3 (placebo) headache days per month during baseline. The change of m/s headache days per 4 weeks during the 12-week observation period was − 4.3 (quarterly), − 4.6 (monthly), and − 2.5 (placebo) days ($p < 0.001$). The difference between active monthly dose and placebo is − 2.1 headache days per 4-week period. The difference in monthly migraine days (secondary endpoint) is − 1.8 days in favor of the monthly fremanezumab dose vs. placebo. In general, the quarterly dose (675 mg) is almost as successful as the monthly dosing paradigm (675/225 mg).

Episodic Migraine Phase II Trial Data

For episodic migraine results from four placebo, controlled randomized double-blind phase II trials are published [16••, 17, 18, 19••]. Of note, the trial with eptinezumab (formerly ALD 403) was aiming at efficacy in weeks 4–8 (primary efficacy endpoint) [17], while all other trials focused on weeks 8–12 for the primary endpoint [16••, 18, 19••]. Trial results are summarized in Table 1.

It is significant to understand that the doses used in these phase II trials will probably not be used for therapy after approval and therefore differences in phase II trials between drugs are not of importance. It is the purpose of phase II studies to define a dose for phase III trials and to deliver proof of concept of the mechanism studied. In detail, 150 mg galcanezumab s.c. twice a month had been used in phase II, but 120 and 240 mg doses s.c. once a month have afterwards been studied in phase III (NCT02614183, NCT02614196). Eptinezumab at a dose of 1000 mg IV quarterly (phase II) but 300 mg doses and lower are studied in later trial stages. Doses of fremanezumab 225 and 625 mg monthly s.c., which had been studied in phase II, have also been used in phase III EM studies, but in addition to a monthly dosing schema, a quarterly dosing scheme has been added (NCT02621931). Only the effective dose of 70 mg erenumab s.c. monthly has made it to phase III (but not the lower doses from phase II due to lack of efficacy), but a dose of 140 mg s.c. has been added in phase III trials [NCT02456740]. For a detailed analysis, please see [1•].

The achievements of these phase II trials for migraine prevention proved that mAbs against CGRP and the CGRP receptor do reduce the frequency of migraine days in EM and that these substances are safe when used in the studied population. Patients with cardiovascular comorbidities or other significant conditions are usually excluded from clinical migraine trials due to possible vascular actions of the drugs under investigation.

At the time of the primary endpoint, all substances were at least in one dose significantly better in phase II than placebo. Difference between highest dose of study drug and placebo range from 2.7 days (fremanezumab) to 1.0 days (eptinezumab). The difference of 50% responders of study drug to placebo has a range from 25% for galcanezumab to 16% for erenumab.

Clinical trial results are affected by baseline migraine days and the number of studies [20]. For example, the higher baseline number of migraine days, the larger is the magnitude of response, which probably explains the higher reduction of migraine days with fremanezumab (baseline 11 days/reduction and – 6 days in weeks 8–12 vs. galcanezumab baseline 6.7 days/reduction and − 4.2 days) [16••, 18].

These phase II data also provide evidence for a group of super responders to CGRP mAb therapy. A 100% reduction of migraine days in weeks 8–12 has been reported from some of the studies. For example, the absolute benefit of eptinezumab over placebo for the parameter 100% response is 24% (41% eptinezumab vs. 17% placebo) [17]. It is important to further analyze this population of super responders and in addition, the non-responder population in order to identify treatment predictors.

No matter which results further subgroup analysis reveal and how they are interpreted, based on positive primary endpoint and safety data, these phase II study results lay basis for the beginning of a new era in the preventative treatment of migraine [21].

Table 1 Summary of primary endpoint results and 50% responder rates in phase II EM migraine prevention trials with CGRP mAbs

	Dose	Baseline migraine days/4 weeks (active/placebo)	Mean reduction of migraine days (weeks 8–12) active/placebo	50% responder rate (weeks 8–12) active/placebo
Galcanezumab	150 mg s.c.; every 14 days	6.7/7.0	− 4.2/− 3.0*	70/45
Eptinezumab	Single 1000 mg I.V.	8.8/8.4	− 5.6/− 4.6* (week 5–8)	77/67
Fremanezumab	625/225 mg s.c.; monthly	11.5/11.5/11.3	− 6.09/− 6.27/− 3.46*	59/53/28 (week 1–12)
Erenumab	70 mg s.c.; monthly	8.6/8.8	− 3.4/− 2.3*	46/30

Phase II long-term open label extension data for a dose of 70 mg erenumab are published up to an observation period of 62 weeks [22]. A total of 373 patients enrolled in the OLE and 307 finished 1-year treatment. Erenumab showed sustained efficacy in the observation period. Patients from the 7 and 21 mg and placebo arms in the DB period came down to the same number of MMD already after a 4-week treatment in OLE phase. The number of MMD day is identical to those in subjects which were from study start (DB phased) in the 70-mg group. Patient-reported outcomes such as HIT-6, MSQ, or MIDAS continued to show beneficial effects during OLE. Nine subjects generated neutralizing antibodies, of which eight only showed transient antibody positivity.

Episodic Migraine Phase III Trial Data

In the next couple of months, a phase III peer-reviewed date from four mAb EM studies and CM studies with galcanezumab and fremanezumab will be published. According to press releases, abstracts, and oral presentations during the IHC conference in Vancouver, all finished phase III trials in EM and CM have met their primary endpoint. Direct comparison of trial results will not be possible since the four trials in EM have different DB treatment duration, and the analysis periods for the primary endpoint are different. For example, galcanezumab and erenumab studies both consist of a 6-month DB study period, while fremanezumab and eptinezumab are only studied for 3 months. In the first published phase III trial, Goadsby et al [23••]. reported data from the STRIVE trial with about 955 subjects in a three-arm study (randomization ratio of 1:1:1).

Baseline migraine days were 8.3/8.2 days and a reduction of 3.7/3.2 in the erenumab groups (140/70 mg) vs. 1.8-day reduction in the placebo group ($p < 0.001$) per 4 weeks in months 4–6 could be achieved. Difference between active 140 mg and the placebo is − 1.9 migraine days along with a reduction of specific migraine medication. Nearly 50% (49.2 [140 mg] vs. 47.1% [70 mg] vs. 29.4% [placebo] had 50% reduction of mean monthly migraine days. Adverse events were mild and in line with data from phase 2 trials.

Safety Data of CGRP Monoclonal Antibodies

Across all trials, the mAbs did not produce a specific signal for a group of > grade 3 or serious adverse events [1•, 22].

The vast majority of adverse events are of mild intensity. The most common adverse event is injection side pain or redness and swelling on the injection side, which is more frequently seen with the active drug than with placebo. Nasopharyngitis has also been reported, but no difference in placebo, and so has back pain and upper respiratory tract infection. Typical mAb adverse effects are different from those with currently available drugs such as weight gain, asthenia, fatigue, depression, or mood swings [24]. Differences between mAbs and currently used preventatives are illustrated in Table 2.

If adverse effect rates are adjusted for 100 patient years, an increase of negative effects cannot be observed with longer treatment duration as in the erenumab OLE phase [22]. The beneficial tolerability of mAbs is reflected by low dropout rates due to adverse effects, or insufficient efficacy in these studies. Tepper et al. report less than a 5% dropout rate in the CM study with erenumab [14••]. Bigal et al. show less than an 8% dropout rate due to insufficient efficacy or tolerability over 3 months, while in a CM trial with topiramate, 24% of subjects dropped out for the same reasons in a 3-month observation period [10••, 25]. Thirteen and 9% (PREEMPT 1 and 2 respectively) of subjects are reported as dropouts in a study with onabotulinum toxin within 6 months [26, 27].

Although there is no indication for alterations in blood pressure or heart rate in mAb study groups, it is important to remind the reader that subjects with a cardiovascular risk were excluded from the trials [16••, 17, 18, 19••]. Since CGRP is a vasodilator, the effects of long-term blockade of this neuropeptide are not known yet, especially under critical conditions such as angina pectoris, myocardial infraction, and stroke [28]. Of note, the typical migraine patient population is not the age group for which the risk for cardiovascular disease is highest. In order to address these concerns, a cardiac safety trial with a small molecule CGRP receptor antagonist was performed some years ago [29]. Acute administration of telcagepant was not different from placebo on total exercise time, or time to 1-mm ST-segment depression in patients with stable angina and reproducible exercise-induced angina. A similar cardiovascular safety trial has been performed with

Table 2 Differences between CGRP mAbs and currently available oral migraine preventative medications

	mAbs for episodic and chronic migraine	Currently available oral medications
Specificity	+	–
Formulation	SC/IV solution	Oral/tablet
Dose titration	–	+
Frequency of intake	Monthly/every 3rd month	Daily
Onset of action	Fast (days)	Slow (weeks)
Side effects (AEs)		
- Effect on weight	–	+
- Mood change	–	+
- Drowsiness/fatigue	–	+
- Cognitive dysfunction	–	+
- Dizziness	–	+

intravenously administered erenumab, and results will be published shortly in a full paper (NCT02575833). So far, no worrying findings with respect to cardiac safety have been made with mAbs. However, from a clinician's point of view, studies on long-term effects of CGRP mAb administration in experimental animals, especially in models where blood flow in the heart or brain is critically reduced, would be greatly appreciated in order to address remaining safety concerns. These studies would allow for the identification of compensatory vasodilatation mechanisms once the CGRP or the CGRP receptor is blocked long term.

Conclusions

CBRP mAbs will provide new therapeutic options for migraine prevention. The key improvements for patients seem to be their tolerability and adverse event profile. Long-term treatment will help us to dissect out their strengths and weakness in the preventative treatment of migraine.

Compliance with Ethical Standards

Conflict of Interest UR is a consultant or scientific advisor for Allergan, Amgen, Autonomic Technologies, Eli Lilly, Electrocore, Novartis, and Teva and has received honorarium from these companies for scientific presentations. H Israel and L Neeb have received honoraria from Pharm Allergan, Eli Lilly (LN), Electrocore Novartis (LN), and Autonomic Technologies. UR, LN, and HI are involved as investigators in clinical trials with mAbs from Amgen, Eli Lilly, Novartis, and Teva without personal remuneration.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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