CNS Drugs (2014) 28:389–399
DOI 10.1007/s40263-014-0156-4

LEADING ARTICLE

Monoclonal Antibodies for Migraine: Preventing Calcitonin Gene-Related Peptide Activity

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Published online: 18 March 2014
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Abstract Calcitonin gene-related peptide (CGRP) is a well-studied neuropeptide of relevance for migraine pathophysiology. Jugular levels of CGRP are increased during migraine attacks, and intravenous CGRP administration induces migraine-like headache in most individuals with migraine. Several CGRP receptor antagonists (CGRP-RAs) were shown to be effective for the acute treatment of migraine, validating the target for the treatment of migraine. However, for a number of reasons, including issues of liver toxicity with chronic use, the development of CGRP-RAs has yet to produce a viable clinical therapeutic. Development of monoclonal antibodies (mAbs) targeting the CGRP pathway is an alternative approach that should avoid many of the issues seen with CGRP-RAs. The exquisite target specificity, prolonged half-lives, and reduced potential for hepatotoxicity and drug–drug interactions make mAbs suitable for the preventive treatment of migraine headaches. This manuscript provides an overview of the role of CGRP in the pathophysiology of migraine, followed by a review of the clinical development of CGRP-RAs. Some basic concepts on antibodies are then discussed along with the publicly disclosed information on the development of mAbs targeting the CGRP pathway.

Key Points

Calcitonin gene-related peptide (CGRP) is relevant to migraine pathophysiology.

CGRP receptor antagonists have demonstrated proof of efficacy for the acute treatment of migraine, but were discontinued because of safety or formulation problems.

Monoclonal antibodies exhibit exquisite target specificity, prolonged half-lives, and reduced potential for hepatotoxicity and drug–drug interactions, and are suitable for the preventive treatment of migraine headaches.

Four monoclonal antibodies targeting CGRP or its receptor are being developed for the preventive treatment of episodic migraine, with two of them also focusing on chronic migraine.

1 Introduction

Calcitonin gene-related peptide (CGRP) is a well characterized peptide occurring in two isoforms, α and β [1, 2]. CGRP belongs to the calcitonin family, which contains four other members: calcitonin, amylin, adenomedullin-2, and adrenomedullin [3]. CGRP is distributed throughout the central and peripheral nervous systems and is often colocalized with other peptides in group C nerve fibers [4–6]. α-CGRP is the most abundant isoform and is found in several areas of the central and peripheral nervous system [7–10]. β-CGRP, which differs from α-CGRP by only three

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amino acids, is primarily, but not solely, located in the gut at the terminal endings of enteric nerves [11].

The importance of CGRP in the pathophysiology of migraine has been well documented [12, 13]. Immunohistochemistry demonstrated that CGRP is mainly produced in the cell bodies of both ventral and dorsal root neurons [14]. Radioimmunology further demonstrated that this molecule is especially common in the trigeminal system, where up to 50 % of the neurons produce it [15]. CGRP is extensively distributed at trigeminal nerve endings, in the trigeminal ganglion, as well as in higher order neurons and in the glia [8, 9, 16, 17]. At the peripheral level (outside of the blood–brain barrier), CGRP release results in vasodilation and inflammation [18]. At central synapses, CGRP is involved in modulating pain transmission [19]. Accordingly, it has been suggested that CGRP is critically positioned on the intersection of peripheral migraine events and central pain modulation [20].

At present, CGRP remains the most actively evaluated, and probably best validated, target in migraine drug research [21]. Clinical proof of efficacy for the acute treatment of migraine has been obtained with several small molecule CGRP receptor antagonists (CGRP-RAs) [22–24], but their development has been complicated by signs of liver toxicity associated with frequent use, or with formulation difficulties [25, 26]. Therefore, much attention has been given to the development of monoclonal antibodies (mAbs) targeting the CGRP pathway, since antibodies have exquisite specificity against their target (e.g., CGRP) and much lower potential for inducing liver toxicity. Herein, we review the current state of development for mAbs targeting the CGRP pathway. To properly contextualize their development, we start by briefly reviewing the pathophysiology of migraine and the relevance of CGRP. We follow by outlining the clinical development of CGRP-RAs for the acute treatment of migraine. We then discuss some basic concepts regarding antibody therapeutics as well as a review of the publicly disclosed information on the development of mAbs targeting the CGRP pathway.

2 The Pathophysiology of Migraine

For many years regarded as a vascular disorder, migraine is actually a prototypical neurological condition [27]. The fundamental initial problem in migraine occurs in the brain [28, 29], although crucial events happen outside of the brain [30, 31], where they are amenable to being addressed by pharmacotherapy [32].

Controversies exist as to whether the first neurological event of migraine takes place in the cortex or in the brainstem [33]. Cortical spreading depression (CSD) is a slowly propagating (2–6 mm/min) wave of sustained neuronal depolarization, which is followed by potent, relatively long-lasting neural suppression [34–36]. CSD is considered to be the electrophysiological substrate of migraine aura [34], and many consider it to be necessary for the development of headache [37]. However, clinical data challenge this assumption since aura occurs in <30 % of migraine patients and most of the symptoms of migraine, including photophobia, phonophobia, and osmophobia, may be explained by abnormal central processing of a normal signal [38].

Migraine is regarded by many as a subcortical disease [39]. Functional brain imaging with positron emission tomography (PET) has demonstrated activation of the dorsal midbrain, including the periaqueductal grey (PAG) and in the dorsal pons, near the locus coeruleus, in studies during migraine without aura [40]. Dorsolateral pontine activation is seen with PET in spontaneous episodic [41] and chronic migraine [42], and with nitroglycerin-triggered attacks [43, 44]. This activation corresponds with the brain region that has been reported to cause migraine-like headache when stimulated in patients implanted with electrodes for pain control [45, 46]. Migraine can develop with pathology in the region of the PAG [47, 48], or with a lesion of the pons [49, 50].

Following cortical changes, brainstem changes, or changes in both, activation of the trigeminal system is thought to occur [51]. When this system is activated, neuropeptides such as CGRP are released from peripheral nerve endings in the cranium [12]. These neuropeptides act at both peripheral sites and within the brain and may play an important role in the generation and maintenance of headache pain and possibly in other migraine symptoms [52].

Pain generation in migraine therefore involves both central activation of pathways relevant to pain as well as peripheral mechanisms. The peripheral events have been characterized as being associated with meningeal neurogenic inflammation consisting of vasodilatation, plasma protein extravasation, and the release of proinflammatory mediators by mast cells [53, 54].

Accordingly, migraine pain may be understood as a combination of altered perception, due to peripheral or central sensitization of stimuli that are usually not painful, as well as the activation of a feed-forward neurovascular inflammatory mechanism in the first (ophthalmic) division of the trigeminal nerve.

3 The Relevance of Calcitonin Gene-Related Peptide (CGRP) for the Pathophysiology of Migraine

Although the original evolutionary function of CGRP was likely related to maintaining vascular homeostasis, it has been speculated that CGRP lost its function during

evolution and should be now viewed as a neuropeptide with an important function in nociceptive transmission [19, 55, 56]. As mentioned, CGRP is widely expressed in the central and peripheral nervous systems where it appears to modulate the function of other neurotransmitters [57]. In the trigeminal ganglion, it is often co-expressed with substance P and 5-$HT_{1B/D}$ receptors [17, 18, 58–60]. The satellite glial cells of the trigeminal ganglion also express CGRP receptors [61].

Following the activation of trigeminal system, CGRP is released at trigeminal nerve endings inducing vasodilation (and edema) [62, 63] and dural mast cell degranulation [20, 64], which both contribute to neurogenic inflammation, a sterile form of inflammation secondary to sensory nerve activation [65]. These peripheral CGRP-containing neurons (in the trigeminal ganglion and elsewhere) are polymodal nociceptors that innervate essentially all peripheral tissues and send primary afferent input to the dorsal horn, trigeminal nucleus caudalis, or nucleus of the solitary tract (which, in turn, project to the brainstem, amygdala, hypothalamus, and thalamic nuclei) [57]. CGRP-containing neurons in the trigeminal ganglion project to the trigeminal nucleus caudalis and C1–C2, where CGRP also acts postjunctionally on these second-order neurons to transmit pain signals from the brainstem to the thalamus [9, 66]. CGRP and its receptors are widely distributed across other parts of the CNS as well, in areas that are relevant to pain and in areas that may not be, such as the cerebellum [8, 67–69]. The function of CGRP in these areas is not well understood. Studies have suggested that CGRP is expressed in areas that could explain migraine-related photophobia [69]. In a model of transgenic mice (nestin/hRAMP1), light-aversive behavior was greatly enhanced by intra-cerebroventricular injection of CGRP and blocked by co-administration of the CGRP-RA olcegepant [70]. Interestingly, as discussed below, controversy exists about whether certain CGRP-RAs penetrate the blood–brain barrier, which raises the possibility that modulation of CGRP outside of the barrier induces modulation of central pathways (such as those inducing photophobia).

A few considerations are relevant in order to understand the theoretical role of CGRP in the pathophysiology of migraine. First, CGRP is ubiquitously distributed in the human body; all vasculature seems to be innervated by CGRP-containing nerve fibers [18]. However, the pool of circulating CGRP is not thought to be relevant to migraine pathophysiology. Instead, data suggest the CGRP released in response to the neurological events of migraine plays a key role in migraine pathophysiology. Second, CGRP is also extensively distributed inside and outside of the blood–brain barrier. Intravenous (IV) administration of CGRP induces migraine attacks in individuals with migraine without crossing the blood–brain barrier [71], while a CGRP-RA (olcegepant) did not affect cerebral hemodynamics in humans [72]. In addition, a study with telcagepant, another CGRP-RA, found that the site of binding in monkeys was mainly at the trigeminal ganglion, which, at least in rodents, is located outside of the blood–brain barrier [73]. In human subjects, PET studies revealed that telcagepant achieved only extremely low receptor occupancy at an efficacious dose (140 mg PO), suggesting that central receptor occupancy was not responsible for its clinical efficacy [74]. These two facts are relevant for understanding the speculated mechanism of action of CGRP mAbs. Antibodies could bind to CGRP released at the trigeminal endings, therefore avoiding the peripheral events of migraine and consequent secondary central sensitization sequelae [75].

4 Challenges in Developing CGRP Receptor Antagonists

The initial approach of targeting CGRP began with the development of small molecule CGRP-RAs. These molecules compete with CGRP for a binding pocket or cleft produced by RAMP1 and the CGRP receptor. Reviews of CGRP-RA studies are provided by Silberstein [25] and Bigal et al. [75].

Five distinct CGRP-RAs have demonstrated proof of efficacy for the acute treatment of migraine, but all were discontinued for a variety of reasons (Table 1). The first CGRP-RA to be developed was olcegepant (BIBN4096BS). Multiple doses were tested and the 2.5-mg dose was considered to be ideal, with a response rate of 66 %, as compared with 27 % for placebo ($P = 0.001$). Onset of effect occurred 30 min post dose [24]. Further development of olcegepant appears to have been discontinued because of difficulties with developing an oral formulation.

Telcagepant (MK-0974) was the first orally available CGRP-RA developed. The phase III program tested doses of 150 and 300 mg. The first pivotal study used 5 mg zolmitriptan as the active comparator and randomized 1,380 patients. Telcagepant (300 mg) had similar 2-h efficacy to zolmitriptan (5 mg); both were superior to 150 mg telcagepant, which was superior to placebo. Tolerability was similar to placebo [22]. Unfortunately, telcagepant development was discontinued because of concerns regarding liver toxicity. Elevations of hepatic enzymes were seen in some participants in a phase II study where telcagepant was given twice daily for the prevention of migraine. Similar elevations were seen in a short-term study of menstrual migraine [25, 26].

A third CGRP-RA, MK-3207, that was 40- to 65-fold more potent than telcagepant [76] was tested in an adaptive

Table 1 Clinical data from phase II and III studies with calcitonin gene-related peptide receptor antagonists

	2 h pain relief (%)	2 h pain free (%)	Adverse events[a] (%)
Olcegepant (phase II) [24]			
2.5 mg	66	44	25
Placebo	27	2	12
Telcagepant			
Study 1 (phase II) [107]			
300 mg	68.1	45.2	35.3
Rizatriptan 10 mg	69.5	33.4	42
Placebo	46.3	14.3	36.2
Drug—placebo	21.8	30.9	−0.7
Study 2 (first pivotal) [22]			
150 mg	50.2	17.2	31.4
300 mg	55.4	26.9	37.2
Zolmitriptan 5 mg	56.1	30.8	50.7
Placebo	26.8	9.4	32.1
Study 3 (second pivotal) [108]			
150 mg	53.8	22.6	30.7
300 mg	56	23.6	34.6
Placebo	32.7	10.4	30.9
MK-3207 (phase II) [23]			
100 mg	52.5	23.7	30.6
200 mg	69	36.2	27
Placebo	36.1	9.8	20.4
BI44370A (phase II) [78]			
200 mg[b]	50.8	21.5	6.2
400 mg	56.2	27.4	9.6
Eletriptan 40 mg	56.5	34.8	17.4
Placebo	18.6	8.6	10
BMS-927711 (phase II) [79]			
10 mg	42	20[c]	[d]
25 mg	37	20[c]	
75 mg	62	31.4	
150 mg	52	32.9	
300 mg	84	29.7	
600 mg	64	24.4	
Sumatriptan 100 mg	71	35[c]	
Placebo	51	15.3	

Modified from Bigal et al. [75]

[a] Methods to assess adverse events varied from trial to trial, so cross-study comparisons should not be performed

[b] Non-significant for the primary endpoint (2 h pain free)

[c] Data inferred from the figure in the original study

[d] Overall adverse event rate not reported

design exploring doses from 2.5 to 200 mg. The 100- and 200-mg doses yielded pain-free rates of 23.7 and 36.2 % (placebo 9.8 %), and pain relief rates of 52.5 and 69 % (placebo 36.1 %) [23]. Development of this CGRP-RA was also discontinued because of concerns related to liver toxicity [77].

A fourth CGRP-RA, BI44370A, was investigated in a phase II trial in 341 patients, where its efficacy was slightly lower than eletriptan, although significantly superior to placebo [78]. Finally, in a recent phase IIb study, a fifth CGRP-RA, BMS-927711, was tested versus placebo or sumatriptan for the acute treatment of migraine [79]. The drug was superior to placebo, although rates of efficacy were numerically inferior to sumatriptan. Tolerability was excellent, but since the study only treated a single attack per patient, the safety in long-term use needs to be further characterized. Plans for future studies with the drug have not been announced [80].

In addition to demonstrating proof of efficacy for the acute treatment of migraine, the CGRP-RA clinical trials also demonstrated the extraordinary tolerability of this class. Other CGRP-RAs are being developed and, at the time of writing, clinicaltrial.gov also lists MK-1622, a phase IIb compound from Merck with doses ranging from 1 to 100 mg for the acute treatment of migraine attacks [81].

5 The Opportunity for Monoclonal Antibodies

Small molecules, such as the CGRP-RAs, offer several clear benefits as a therapeutic modality, such as the flexibility in formulation options, including oral delivery. The manufacturing process of small molecules is also well defined and less expensive compared with biologics.

However, mAbs possess several clear advantages over small molecules. Although more limited in terms of delivery route, mAbs can be designed to have excellent target specificity, thus avoiding off-target toxicities, as demonstrated by their ability to differentiate between closely related family members (e.g., CGRP vs. amylin or adrenomedullin) [82]. In addition, most mAbs have reasonably long terminal half-lives. This extended pharmacokinetic profile often results in less frequent dosing, which mitigates the need to deliver them through parenteral routes [83]. For example, while typical migraine preventive medications need to be dosed once or twice every day [84], an mAb could be administered once a month or even less frequently. Accordingly, the inconvenience of parenteral administration may be offset by the convenience of infrequent dosing.

As mentioned earlier, as mAbs are biologics, or therapeutic proteins, they are generally not subject to hepatic processing to potentially toxic metabolites. Instead, they are catabolized by normal processes to endogenous amino acids which are excreted through the kidneys or liver [85]. These metabolites become indistinguishable from normally circulating peptides and amino acids and therefore

generally pose fewer safety concerns. In contrast, small molecule metabolites need to be extensively characterized as they can sometimes pose toxicological risks [85].

From a safety and tolerability perspective, mAbs offer great potential benefit over small molecules, whose metabolic profile in humans is often not fully understood until clinical testing is underway. In many cases, any toxicological issues with mAbs are due to diminished pharmacology, not to off-target effects as often seen with small molecules [86]. What this means is that a potential mAb toxicity can be often predicted and managed, depending upon the effect of prolonged target inhibition [85, 87]. Accordingly, safety concerns regarding anti-CGRP mAbs would be derived from CGRP inhibition (and therefore be non-specific to antibodies), as well as from antibody administration. Since CGRP is a vasodilator, four major cardiovascular effects could be of concern with CGRP inhibition: medication-induced hypertension, counterbalancing the effect of anti-hypertensive drugs that have vasodilatory properties, inhibition of stress (or ischemia)-induced vasodilation, and impairment of cardioprotective mechanisms. This topic has been reviewed elsewhere [75]. The available data is insufficient to rule out all cardiovascular safety concerns with inhibiting CGRP function. But no other class of migraine medication, including those inducing vasoconstriction, such as ergotamine and the triptans [88–90], has been so intensively and exhaustively tested in this regard.

Furthermore, CGRP exhibits a range of biological effects on tissues, including those associated with gastrointestinal, respiratory, endocrine, and central nervous systems [91, 92], and wound healing [93]. These safety concerns would be non-specific to the mechanism of inhibition (small molecules or antibodies), and available clinical data have not identified relevant safety concerns in any of these areas.

As for concerns related to antibodies, they would include infusion reactions and site administration reactions, as well as immunological effects. A potential liability is derived from the long half-lives of antibodies. Discontinuation would not yield immediate clearance of the molecule.

Findings for current developments are described below. Table 2 summarizes important differences in the preclinical development of small molecules and mAbs.

6 Monoclonal Antibodies Targeting the CGRP Pathway: Review of Current Development

At the time of writing, there are three mAbs directed against CGRP in various stages of clinical development: LY2951742, developed by Arteaus Therapeutics; ALD403, developed by Alder Biopharmaceuticals; and LBR-101, developed by Labrys Biologics. In addition, there is one mAb directed against the CGRP receptor in development by Amgen (AMG 334). Table 3 contrasts relevant aspects of their development.

6.1 ALD403

ALD403 is a humanized antibody being developed by Alder Biopharmaceuticals (http://www.alderbio.com/) for the preventive treatment of episodic migraine. A unique feature of this program is that the antibody is produced using yeast, not mammalian cells. According to the company, the process can yield faster production, with subsequent economic advantages [94].

ALD403 was first tested in phase I, in a two-part, placebo-controlled, single ascending dose study conducted to evaluate the safety and tolerability of two different formulations, administered subcutaneously and intravenously. In the first part of the study, healthy volunteers were enrolled and followed for 12 weeks after ALD403 administration, with pharmacokinetic and pharmacodynamic assessments conducted. In the second part of the study, ALD403, placebo or sumatriptan were administered [95].

In March of 2013, the company announced the dosing of the first patients in a proof-of-concept clinical study [96]. The study tested 160 patients with episodic migraines (who had between 4 and 14 days of headache). According to clinicaltrials.gov, in this phase I study, a single IV dose was given once and contrasted with placebo. The primary aim of the study was to assess the safety of a single exposure of ALD403 for 24 weeks after administration. The study also aimed to assess the pharmacokinetics of the drug and to explore the efficacy of ALD403 in terms of change in frequency of migraine days compared with baseline. The estimated primary completion date is listed as November of 2013. To date, results have not been disclosed [97].

6.2 LY2951742

LY2951742 is a humanized mAb that binds CGRP, in development by Arteaus Therapeutics (http://www.arteaus.com/) for the preventive treatment of episodic migraine.

The LY2951742 phase I program has been completed. In total, 56 subjects were treated in the study. In the first phase of the program, the safety and tolerability of LY2951742 was examined following escalating single doses. After the initial phase was completed, a repeat-dose expansion phase was initiated, where subjects received repeat doses of LY2951742 every other week for 6 weeks. Safety, tolerability, pharmacokinetics, and pharmacodynamics were assessed in this phase of the study. LY2951742 was reported to be well tolerated and showed linear pharmacokinetics with a terminal half-life ($t_{½}$)

Table 2 Preclinical studies required for development

Study/assay	Small molecule	mAb	Comments
Immunogenicity (ADA, NAb)	No	Yes	
Drug–drug interaction	Yes	No	Only warranted for mAbs when MOA would suggest concern
hERG assessment	Yes	No	Cardiovascular safety to be assessed in vivo studies for mAbs
Tissue cross reactivity	No	Yes	
Metabolism	Yes	No	
Determining MTD	Yes	Yes	Can be challenging for mAbs
Genetoxicity	Yes	No	
Carcinogenicity studies	Yes	No	Not generally needed for mAbs unless MOA would suggest concern

Modified from Bigal et al. [75]

ADA anti-drug antibody, *hERG* human ether-a-go-go, *mAbs* monoclonal antibodies, *MOA* mechanism of action, *MTD* maximum tolerated dose, *NAb* neutralizing antibody

Table 3 Comparison of monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway

	ALD403	LY2951742	AMG 334	LBR-101
Target	CGRP with a humanized antibody	CGRP with a humanized antibody	CGRP receptor with a human antibody	CGRP with a fully humanized antibody
Migraine state	Episodic	Episodic	Episodic and chronic	Episodic and chronic
Dosing and phase	Single dose level (phase Ib/IIa)	Single dose level (phase IIa with positive data being reported)	Dose-ranging (phase IIb)	Dose-ranging (phase IIb)
Form of administration in phase II	Intravenous	Subcutaneous	Subcutaneous	Subcutaneous
Phase II dosing frequency	Only once over the course of the study	Twice per month for 3 months	Once per month for 3 months	Once per month for 3 months

ranging from 25 to 30 days and a time to maximum plasma concentration (t_{max}) from 7 to 14 days [98].

Arteaus recently completed a phase IIa, double-blind, randomized, placebo-controlled trial in patients with episodic migraine, testing 150 mg of LY2951742 against placebo, delivered by subcutaneous (SC) injection once every other week for 12 weeks, with a 12-week follow-up period. The primary outcome measure listed is the mean change from baseline in the number of migraine headache days in a 28-day period. Arteaus was recently acquired by Eli Lilly and, at the time of the announcement, the study was reported to have achieved primary and secondary endpoints [99], suggesting validation for the use of CGRP mAbs in migraine.

6.3 AMG 334

Amgen is developing AMG 334, a fully human antibody for the prevention of episodic and chronic migraine. Unlike the other antibodies discussed, AMG 334 targets the CGRP receptor, not the free peptide [100]. Three phase I studies have been initiated to test the safety and tolerability of AMG 334. In one completed study, approximately 68 healthy subjects and migraine patients were administered single ascending doses of AMG 334 by IV or SC routes. Another phase I study listed is testing multiple doses of AMG 334 in both healthy subjects and migraine patients. Three dose levels are being examined, all administered via SC injection, testing the safety, pharmacokinetics and pharmacodynamics following multiple injections [101, 102]. A phase I study is also being conducted in women with hot flashes associated with menopause.

AMG 334 is also currently enrolling two phase IIb studies, one in episodic and the second in chronic migraine. In the episodic migraine study, patients are randomized to receive AMG 334 (one of three dose groups) or placebo via SC injection. The primary endpoint for this study is the change in monthly migraine days from baseline in the last 4 weeks of a 12-week, double-blind treatment phase. Eligible patients have had a history of migraine for at least 12 months prior to screening and suffer from between 4 and 14 migraine days a month [103].

Clinical data from the AMG 334 phase I program have not been publicly presented.

6.4 LBR-101

LBR-101 is a fully humanized anti-CGRP mAb. In contrast with the other mAbs in development, LBR-101 is not only

being developed for the preventive treatment of episodic migraine, but also for the prevention of chronic migraine, in a dual phase IIb program. Data for LBR-101 have been disseminated more extensively than for the other mAbs, and are summarized here.

The preclinical profile of LBR-101 has been studied in single- and repeat-dose studies in both rats and cynomolgus monkeys. In all studies, LBR-101 was extremely well tolerated at doses up to 300 mg/kg/week for 14 weeks.

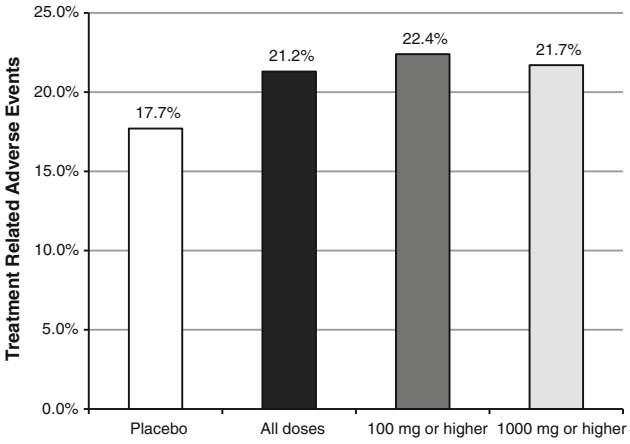

Fig. 1 Proportion of subject with treatment-related adverse events in LBR-101 intravenous phase I studies. Modified from Bigal et al. [105]

Because CGRP is a potent vasodilator, the cardiovascular safety of LBR-101 in the monkey was also examined in a repeat-dose study and in a dedicated single-dose safety pharmacology study. In neither case did any evidence of blood pressure changes emerge, nor any ECG abnormalities. The terminal half-life of LBR-101 in the monkey is estimated between 10 and 26 days (IV and SC routes of administration) [104].

The IV clinical pharmacokinetics of LBR-101 have been studied extensively in five different phase I trials, with doses ranging from 10 to 2,000 mg as 1-h IV infusions [105]. Maximum plasma concentrations (C_{max}) were reached shortly after the end of infusion. The median time to C_{max} (t_{max}) ranged from 1.0 to 2.0 h, followed by a multiphasic decline. The $t_{½}$ ranged from 39.4 to 48.3 days, and the increase in area under the curve appeared to be greater than dose proportional between 10 and 30 mg and to be approximately dose proportional between 30 and 1,000 mg. The SC clinical pharmacokinetics were characterized in a separate phase I study.

6.5 Safety

As an IV formulation, LBR-101 was administered to 94 subjects, while 45 received placebo. Doses ranged from 0.2 to 2,000 mg given once (day 1), as a single IV infusion, or

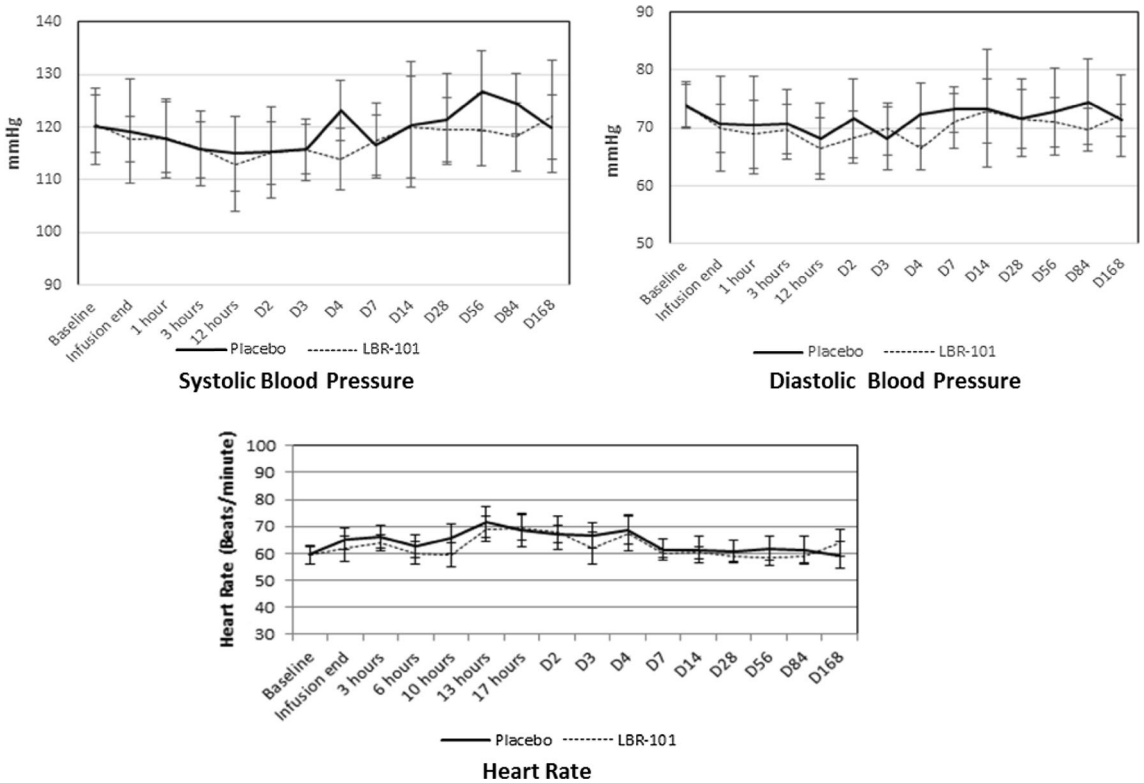

Fig. 2 Cardiovascular parameters in subjects receiving LBR-101 or placebo. *D* days

up to 300 mg given twice (day 1 and day 14). Data are fully presented in Bigal et al. [106]. Across the broad range of doses, IV LBR-101 was well tolerated and overt safety findings did not emerge. Figure 1 summarizes the overall incidence of adverse events by dose. Participants receiving placebo reported an average of 1.3 treatment-emergent adverse events (related or not to study medication). Across all LBR-101 doses, treatment-related adverse events (TRAEs) happened in 21.2 % of subjects receiving LBR-101, compared with 17.7 % in those receiving placebo. At doses of 100 mg of LBR-101 or higher, TRAEs happened in 22.4 % of participants. At doses of 1,000 mg or higher, they happened in 21.7 % of participants [105].

LBR-101 does not appear to be associated with any clinically relevant patterns of change in vital signs (systolic and diastolic blood pressure, temperature and heart rate). Clinical laboratory findings were similar across placebo and LBR-101. In particular, liver function abnormalities, defined as any post-dose value outside the normal test range, were not observed for aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, and gamma-glutamyl transferase (GGT) among subjects receiving any of the studied doses of LBR-101 [105].

The sustained hemodynamic effects of CGRP inhibition following LBR-101 were assessed via a double-blind, placebo-controlled, single-dose, dose-escalation study, where 31 women (mean age 56 years) were randomized to receive placebo or LBR-101 at doses ranging from 300 to 2,000 mg; the latter represents a supra-therapeutic exposure. Participants were confined for 7 days and followed after discharge for 168 days. Continuous cardiac telemetry was initiated 2 h before infusion and continued until 8 h after completion of infusion. All physical and hemodynamic assessments and ECGs were conducted six times during day 1, daily during the first 3 days of confinement, 1 week after discharge (day 14), and then 1, 2, and 3 months after the LBR-101 infusion. No clinically relevant changes in systolic or diastolic blood pressure, heart rate, or ECG parameters (RR, PR, QRS, or QTcF) were observed when comparing baseline with post-dose time points, or between groups for any parameter or time point. No statistically significant differences or clinically relevant abnormalities were seen when comparing parameters obtained at t_{max} versus baseline, or t_{max} versus any other time point (Fig. 2) [104].

7 Conclusion

Four mAbs are currently being developed for migraine prevention. The four mAbs target episodic migraine, while two (LBR-101 and AMG 334) target chronic migraine as well. Two of them (AMG 334 and LBR-101) are currently undergoing testing using multiple doses in phase IIb for their specific development. One (LY2951742) reported positive topline results from a phase IIa study. No reports of liver toxicity have been disclosed. Tolerability was published for LBR-101 and seems to be excellent. Cardiovascular effects have not been reported. Based upon the emerging data, mAbs targeting the CGRP pathway are a promising new drug class that may provide a valuable new option for clinicians aiming to relieve the burden of individuals with episodic or chronic migraine.

Disclosure The authors are full time employees of Labrys Biologics, a company developing an mAb against CGRP (LBR-101).

No funding was received for writing this article. The review represents the authors' own work and no medical writers were involved in its planning or execution.

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