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Monoclonal CGRP Ligand/Receptor Antibodies for the Preventive Treatment of Episodic and Chronic Migraine

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Abstract

Four monoclonal antibodies are currently in development for the preventive treatment of episodic and chronic migraine, one of them against the CGRP receptor and three against the CGRP ligand. These four antibodies are, in order of development, galcanezumab, eptinezumab, fremanezumab, and erenumab, the first three against the CGRP ligand and the last one against the CGRP receptor. Published, phase II, randomized, double-blind, placebo-controlled studies suggest similar efficacy of the antibodies. Tolerability in terms of adverse-event occurrence appears good while long-term safety of CGRP blockade needs further investigation.

Keywords: CGRP; CGRP Ligand; CGRP Receptor; Monoclonal Antibodies; Episodic Migraine; Chronic Migraine; Preventive Treatment; Eptinezumab; Erenumab; Fremanezumab; Galcanezumab; Onabotulinumtoxin A

Introduction

CGRP or calcitonin gene-related peptide is a neuro peptide involved in an inflammatory mechanism, referred to as neurogenic inflammation [1]. It is an inflammatory reaction in peripheral tissue caused by the local activation of nociceptive nerve fibers [2]. The nociceptive nerve fibers are the non-myelinated C-fibers and the thinly myelinated A-fibers. Upon activation, they release so-called neuropeptides locally in the tissue, resulting in a local, particularly perivascular, inflammation. The nerve fibers also release the neuropeptides in the dorsal horn of the spinal cord and its rostral extension in the brainstem, the trigeminal nucleus caudalis. In the central nervous system, the release of the peptides results in signal transmission from the primary to the secondary nociceptive nerve fibers [3]. The latter nerve fibers form the spinothalamic and trigeminothalamic tracts, the last one particularly relevant in the context of headache. The relevant neuropeptides mostly concern substance P and CGRP and both contribute to the local inflammatory reaction, each in its own way. Acting predominantly at the microcirculatory level, substance P increases vascular permeability and CGRP causes vasodilation [3]. The peptides set a cascade into action that ultimately involves a variety of cellular elements and a great number of humoral mediators [4]. It has been postulated that this local inflammatory reaction in migraine occurs in the dura mater [5], although there is no clinical evidence to support this notion. Dated studies in migraine patients, examined during the presence of headache, suggest the inflammation to occur in the extracranial tissues [6]. Specifically related to CGRP, blood drawn from the external jugular vein showed an elevated level during migraine headache [7], with normalization after administration of sumatriptan and resolution of the pain [8]. The external jugular vein drains blood particularly from the extracerebral tissues, predominantly extra cranial but also somewhat intracranial, that is, from the dura mater. The study that showed an elevated level of CGRP in blood drawn from the external jugular vein did not show that for substance P [7]. Drug development targeting the substance P pathway has also not generated effective treatments for migraine, either abortively or preventively [9]. This is very different from the drug development targeting the CGRP pathway, which has generated positive results regarding abortive migraine treatment with small molecule CGRP-receptor antagonists. This particular class of medications is also referred to as gepants and includes, among others, olcagepant, telcagepant, rimegepant, ubrogepant, and atogepant. The development of the first two has been abandoned because of non-oral administration and hepatotoxicity, respectively. Rimegepant and ubrogepant are still in development for the abortive treatment of migraine and atogepant for preventive migraine treatment. The monoclonal antibodies against the CGRP ligand or CGRP receptor have been in clinical development for preventive migraine treatment since 2012. It concerns here three antibodies against the CGRP ligand and one against the CGRP receptor. The antibody against the CGRP receptor is a human antibody, while the other three are humanized antibodies. All four of

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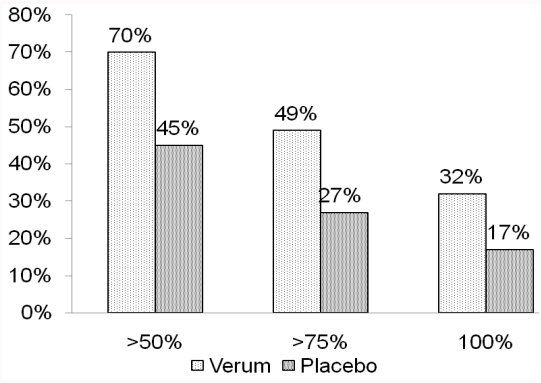

Figure 1: The effect of galcanezumab, 150 mg subcutaneously every 2 weeks, *versus* placebo on the number of migraine headache days during the 3-month treatment period in patients with episodic migraine: results of the ≥ 50%-, ≥ 75%-, and 100%-responder analysis as presented in reference 10.

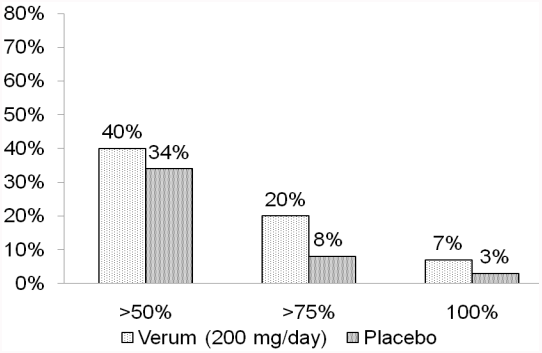

Figure 2: The effect of topiramate, 100 mg orally twice daily, *versus* placebo on the number of migraine attacks during the 3-month treatment period in patients with episodic migraine: results of the ≥ 50%-, ≥ 75%-, and 100%-responder analysis as presented in reference 12.

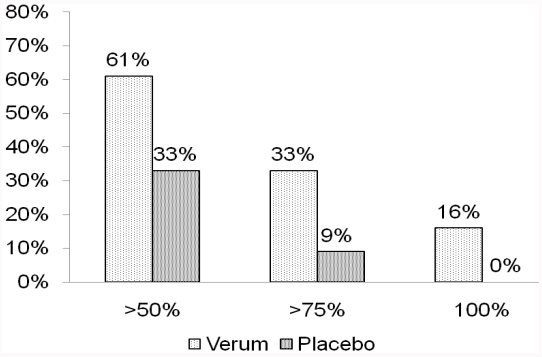

Figure 3: The effect of eptinezumab, 1000 mg intravenously, *versus* placebo on the number of migraine headache days during the 3 months following infusion in patients with episodic migraine: results of the ≥ 50%-, ≥ 75%-, and 100%-responder analysis as presented in reference 13.

them are administered parenterally, one intravenously and three subcutaneously, either monthly or quarterly. The subcutaneously administered antibodies are expected to obtain FDA approval and come to market in 2018. Below, the results of the published, phase II, randomized, double-blind, placebo-controlled studies are presented.

Galcanezumab

Galcanezumab is a humanized monoclonal antibody against the CGRP ligand that is administered subcutaneously [10]. The proof-of-concept study of this class of medications for migraine prevention was conducted with this particular antibody. The study was conducted in patients with episodic migraine, that is, migraine with and/or without aura and in total less than 15 headache days per month [11]. The medication was administered subcutaneously in a dose of 150 mg, every 2 weeks during a period of 3 months. Prior to the treatment, the patients completed a 1-month prospective baseline to establish the number of migraine headache and headache days per month, as well as the migraine attack frequency. All three outcome measures revealed a statistically significant improvement from baseline to the third month *versus* placebo (p values 0.003, 0.012, and 0.005, respectively). (Figure 1) shows the results of the responder analysis, based on the number of migraine headache days during the 3-month treatment period, separately for the ≥ 50%- ≥ 75%-, and 100%- responders. The results revealed a statistically significant migraine improvement in comparison to placebo, which by definition means a specific pharmacological effect. However, what is missing is a context due to the lack of an active comparator in the study. Comparing across studies, as opposed to comparing within a study, is not scientifically valid but it is the only way to obtain context here. Hence, for comparison Figure 2 presents the results of a study with topiramate for the preventive treatment of episodic migraine, in which a similar responder analysis was applied [12]. With the caveat, as mentioned, that comparing across studies is not scientifically valid the results do suggest that galcanezumab is much more effective than topiramate in the preventive treatment of episodic migraine. Given the differences in placebo response, one can only consider the deltas for comparison, that is, the differences between the verum and placebo responses. For galcanezumab, the differences in all three response categories (25%, 22%, and 15%) are considerably greater than for topiramate (6%, 12%, and 4%) but, nevertheless, this is only a suggestion of superior efficacy.

Eptinezumab

Eptinezumab is also a humanized monoclonal antibody against the CGRP ligand; it is yeast based and administered intravenously [13]. The medication was given to a group of patients with episodic migraine with and/or without aura, comparable to those in the galcanezumab study. It was administered once in a dose of 1000 mg intravenously and the efficacy was determined over the 3 months following the infusion. Related to the change from baseline in the number of migraine headache days per month, the medication was statistically significantly better than placebo for the first and second month after the infusion (p values 0.001 and 0.031, respectively) but not for the third month (p value 0.065). The effects on the number of headache days per month and the frequency of migraine attacks were numerically better than placebo but not so statistically. Figure 3 shows the responder analysis of the study results, based on the number of migraine headache days for the entire, 3-month period following the infusion. Comparing those results with the responder-analysis results of the galcanezumab study (Figure 1), the difference between the two studies in terms of placebo response is striking (0% to 33% *versus* 17% to 45%). The much higher placebo response in the galcanezumab study is possibly due to the fact that the medication was administered twice monthly, as opposed to the one-time administration of eptinezumab. The deltas, however, are remarkably similar, that is, 25% and 28%, respectively, for the ≥ 50%-response category, 22% and 24%, respectively, for the ≥ 75%-response category, and 15% and 16%, respectively, for the 100%-response category. Hence, it is tempting to state that the eptinezumab study to a great extent confirms the results of the galcanezumab study, both qualitatively and quantitatively.

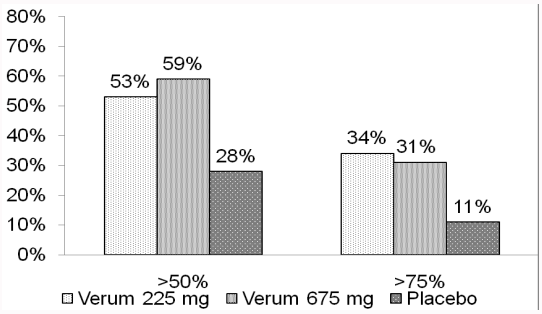

Figure 4: The effect of fremanezumab, 225 or 675 mg subcutaneously per month, *versus* placebo on the number of migraine headache days during the 3-month treatment period in patients with episodic migraine: results of the ≥ 50%- and ≥ 75%-responder analysis as presented in reference 14 (addendum).

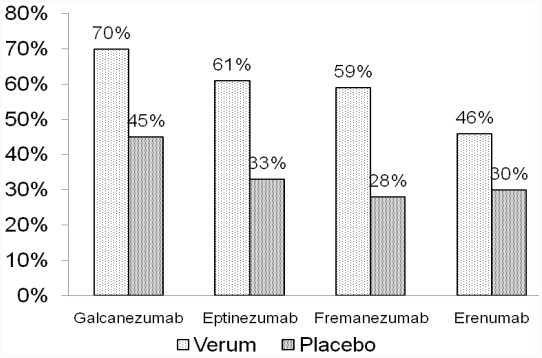

Figure 5: The effect of the four monoclonal antibodies against CGRP ligand/receptor *versus* placebo in the preventive treatment of episodic migraine with and/or without aura, on the basis of the ≥ 50%-responder analysis as presented in references 10, 13, 14 (addendum), and 15.

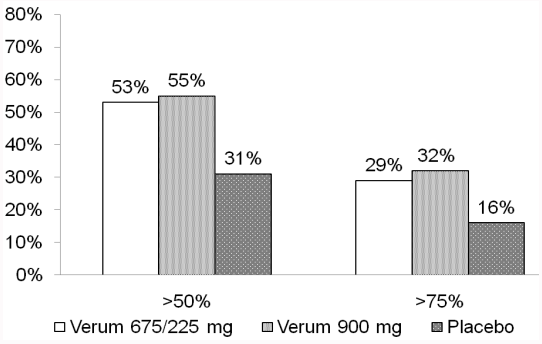

Figure 6: The effect of fremanezumab, 900 mg subcutaneously per month or 675 mg subcutaneously the first month and 225 mg subcutaneously per month the two following months, *versus* placebo on the number of days with moderate or severe headache during the third month of treatment in patients with chronic migraine: results of the ≥ 50%- and ≥ 75%-responder analysis as presented in reference 16 (addendum).

Fremanezumab

Fremanezumab is a monoclonal antibody comparable to galcanezumab because it is also a humanized antibody against the CGRP ligand that is administered subcutaneously [14]. In the study in episodic migraine patients, the medication was administered monthly for 3 months in a dose of 225 mg or 675 mg subcutaneously. Both doses gave comparable results in comparison to placebo in terms of a statistically significant improvement from baseline in the number of migraine headache and headache days per month during the 3 months of treatment (p values 0.001 or less). That both doses are similarly effective is also evident from the results of the responder analysis for which only the ≥ 50%- and ≥ 75%-response categories are available (Figure 4). When comparing those results with the ≥ 50%- and ≥ 75%- response categories of eptinezumab (Figure 3), it is remarkable that the verum as well as placebo responses are similar. Hence, also here it is tempting to state that fremanezumab and eptinezumab are similarly effective in the preventive treatment of episodic migraine with and/or without aura.

Erenumab

Erenumab, lastly, is a human monoclonal antibody not directed against the CGRP ligand but against the CGRP receptor, which like galcanezumab and eptinezumab is administered monthly by subcutaneous injection [15]. In the episodic migraine study, the medication was given for 3 months in monthly doses of 7 mg, 14 mg, and 70 mg and only the highest dose proved efficacious. It generated a statistically significant separation from placebo during the 3 months of treatment for the number of migraine headache days per month (p values 0.029, 0.029, and 0.021) but not for the frequency of migraine attacks. Figure 5 shows the results of the ≥ 50% -responder analysis for erenumab together with those of the other three antibodies. Again with the caveat that comparing across studies is not scientifically valid, it appears that the antibodies are similarly effective, with deltas of 28% (eptinezumab), 25% (galcanezumab), 23% (erenumab), and 21% (fremanezumab).

Chronic migraine

Apart from episodic migraine, the drug development under discussion also concerns chronic migraine. Since the registration with the FDA of onabotulinumtoxinA for the preventive treatment of chronic migraine, separate studies are required for this indication. In contrast to chronic migraine, studies of onabotulinumtoxinA in episodic migraine did not demonstrate preventive benefit. Chronic migraine, however, does not differ from episodic migraine except in headache frequency, which in chronic migraine is 15 or more days per month [11]. Hence, it is questionable whether onabotulinumtoxinA actually treats migraine and it has been suggested, instead, that it treats an associated condition, a so-called comorbidity, which accounts for the high frequency of the headaches in chronic migraine [16]. The situation appears different with the antibodies against the CGRP ligand and CGRP receptor because a study with fremanezumab has also demonstrated efficacy in the chronic form of migraine [17]. In this study, the efficacy of two dose regimens of the medication was determined: 900 mg subcutaneously monthly and 675 mg subcutaneously the first month with 225 mg subcutaneously the subsequent two months. Both dose regimens rendered a statistically significant improvement *versus* placebo in the first month of treatment on migraine headache days per month (p values 0.001 and 0.012, respectively) and headache days per month (p values 0.001 and 0.012, respectively). The 900-mg dose regimen also statistically significantly improved the number of migraine headache and headache days per month in the third month (p values 0.041 and 0.004, respectively) and the number of headache days per month in the second month (p value 0.026). The responder analysis of this study, as presented in Figure 6, focused on days with moderate or severe headache, which generally generates similar results to migraine headache days as the outcome variable. Apart from showing the medication to be effective in chronic migraine, the results also suggest its efficacy in this condition to be similar to that in episodic migraine, with the caveat that higher doses were used, that is, 900 mg

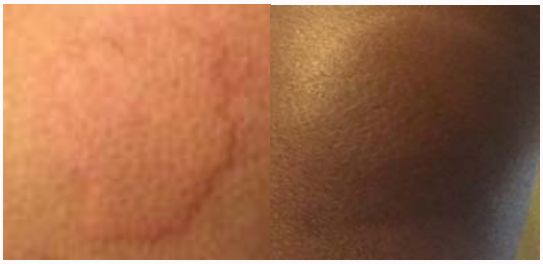

Figure 7: Two examples of injection site reactions with subcutaneous administration of monoclonal antibodies against the CGRP ligand/receptor: an inflammatory reaction and an urticarial reaction.

and 675/225 mg monthly in chronic migraine versus 225 mg and 675 mg monthly in episodic migraine.

Safety and tolerability

In the above studies, adverse events were collected, as is standard in clinical trials, regardless of their causal relation to the study medication. Also, twice monthly or monthly, blood pressure was measured and routine blood testing was performed, including hematology, blood chemistry, and antibodies, as well as Electro Cardiography (ECG). Systematic deviations, for example in blood pressure, liver enzymes, or ECG, were not observed with any of the CGRP antibodies. Regarding tolerability, the adverse-event occurrence is similar with the antibodies as it is with placebo, that is, 46% to 72% in comparison to 40% to 67%. An exception concerns the injection-site reactions with the subcutaneously administered antibodies, which, as could be expected, occur at a higher frequency with the antibodies than with placebo (Figure 7). Allergic reactions were rarely observed and anaphylactic reactions have not been reported to date for any of the four antibodies.

Conclusion

The results of the studies presented above, although preliminary as phase II studies are, suggest that, after decennia of research, medications are now being developed that seem to specifically address a mechanism related to the migraine headache, at least in as much as it is currently understood.

Acknowledgement

As a principal investigator, professor Spierings was involved in all referenced studies with the monoclonal antibodies against the CGRP ligand/receptor for the preventive treatment of episodic or chronic migraine. Consequently, he received research grants from Alder Biopharmaceuticals (eptinezumab), Amgen (erenumab), Eli Lilly & Company (galcanezumab), and Teva Pharmaceuticals (fremanezumab). He also received research grants from Allergan for participation in studies with onabotulinumtoxinA, ubrogepant, and atogepant and from Bristol Myers Squibb for a study conducted with rimegepant. He wrote the present manuscript without external involvement or financial support.

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