Treatment with anti-CGRP (receptor) antibodies for migraine: can we predict effectiveness?

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Chapter 9
General discussion

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Migraine is a highly disabling disease characterized by recurrent, moderate to severe headache attacks, accompanied by symptoms such as photo- and phonophobia, nausea and/or vomiting. It is classified as the second most debilitating disorder expressed as years lived with disability.[1] Many prophylactic treatment options exist, but a large proportion of patients does not respond to any of these drugs or has debilitating side effects. Although these treatments have been proven to be effective in migraine, they all have different sites of action, and their mechanism of action in preventing migraine remains unclear.

In the last decades major progress has been made in discovering part of the pathophysiology of migraine. The discovery of the involvement of calcitonin gene-related peptide (CGRP) in migraine pathophysiology has led to the development of the first migraine-specific prophylactic drugs targeting this peptide or its receptor. Although these drugs provide an improvement for many migraine patients, they are unfortunately not successful in every migraine patient.

Currently, it is unknown which factors determine whether a patient is a responder to a particular type of drug. As it is recommended to treat patients with a certain prophylactic drug at least 2-3 months on a stable dose before assessing treatment response, finding a successful treatment can be a time consuming process. Moreover, there are highly treatment refractory patients, i.e. patients that do not respond to any of the available treatment options. Therefore, major advancements in migraine care are necessary. This requires increasing the insight in the treatment response over time, understanding the mechanism of action of the current pharmacological treatments, and identifying patient-specific factors that influence or can predict the clinical response to treatment. This may ultimately lead to the development of more effective treatment options.

Part I Efficacy and safety of treatment with anti-CGRP (receptor) antibodies

Treatment effectiveness

Randomized clinical trials of prophylactic migraine treatment generally present the number of patients with ≥50% reduction in monthly migraine days (MMD), as this is often perceived as a meaningful response to prophylactic drugs. As a rule of thumb for clinical practice, preventive migraine treatment in general may lead to approximately 50% reduction in monthly migraine days in half of patients.Even though this cut-off point of 50% reduction in monthly migraine days is clear and useful in clinical trials and other scientific research, in clinical practice it seems less suitable. Firstly, this cut-off value may be too strict as many patients who consider treatment to be effective will not fulfill this 50% criterion. Patients with for example 45% reduction in monthly migraine days will not be considered non-responders in clinical practice and probably would like to continue their treatment. Secondly, the ≥50% responder rate in clinical trials is often assessed in either the last month of treatment or as an average response over several months, meaning that each month the group of patients that reaches this ≥50% responder rate will be different. For an individual patient in clinical practice the consistency of the response, meaning the % of reduction of MMD for each month, is more important to decide whether treatment is effective and should be continued. Thirdly, migraine is known to have a natural monthly fluctuation and, therefore, a period of 3 month treatment may be too short to have a thorough estimation of positive effectiveness of prophylactic treatment and a longer period may be required to decide that medication is not effective and should better be stopped.

In **chapter 2** we provided an overview of the clinical response to erenumab during a 6-month follow-up period in real world data. Both monthly response and the consistency in response were assessed in patients with high frequent episodic or chronic migraine, who were highly treatment refractory, meaning that they previously failed on ≥ 4 prophylactic treatments. We observed a wide range in migraine reduction, and on an individual level a low consistency of response over the whole period of several months. While between 22% and 43% of patients had ≥50% reduction in MMD in at least one month of this 6 month follow-up, 36% of patients had ≥50% reduction in 3 out of 6 months, and only 6% of patients had ≥50% MMD reduction in all 6 months. Between 47% and 59% had ≥30%

reduction in MMD in at least one month during this 6 month follow-up, 60% of patients had ≥30% reduction in 3 out of 6 months, and only 24% of patients had ≥30% MMD reduction in all 6 months. To establish whether a patient responded to treatment, the emphasis should be on a consistent response over time, while still considering the natural fluctuation in monthly migraine days. For this reason we propose to consider refractory patients who failed on ≥ 4 prophylactics a responder in case of ≥30% MMD reduction for at least half of the treatment period. This proposition was adopted by Zorginstituut Nederland, the Dutch National Health Authority, when deciding on including the anti-CGRP (receptor) antibodies in the standard health insurance package for chronic migraine patients who failed on previous preventive treatments including botulin-toxin-A.[2,3]

To determine clinical response to prophylactic migraine treatment, the use of an E-headache diary is strongly advised. Retrospective self-reported MMD are highly subject to recall bias.[4] Below the number of 8 MMD patients tend to underestimate, whereas above 8 MMD patients tend to overestimate their number of migraine days.[5] This is of utmost importance as for the definition of chronic migraine the cut off value of MMD is 8 or more days.[6] In addition, it is important to incorporate patients' perception of impact of migraine and treatment effectiveness, using a validated instrument or by simply asking for patients' perception of treatment effect. Moreover, as -anti-CGRP treatment is costly, healthcare insurance companies will require detailed information on diagnosis, previous use of prophylactics, indication, and effectiveness of anti-CGRP (receptor) antibodies for reimbursement.

Treatment safety

Migraine is associated with an increased risk of cardiovascular disease and, therefore, it is important that newly developed treatment does not increase this risk any further. Although CGRP does not seem to have a role in the physiological regulation of normal blood pressure, there is evidence that it provides a key compensatory mechanism against elevating blood pressure.[7] Thus, a potential risk of hypertension may arise when CGRP is blocked.

Chapter 3 presents the results of a prospective study regarding blood pressure of migraine patients treated with erenumab and fremanezumab at the Leiden Headache Center during one year follow-up. Already at the first follow-up visit after three months of treatment, an increase in both mean systolic and mean diastolic blood pressure was observed. The subgroup

analyses suggested a larger and more consistent blood pressure effect in the erenumab subgroup than in the fremanezumab subgroup. Four patients without hypertension before starting treatment with erenumab, were prescribed antihypertensive drugs in the course of treatment. Fortunately, the majority of patients did not require antihypertensive treatment. Additionally, in the study from **chapter 4** it was demonstrated that erenumab did not influence resting dermal blood flow (data not shown). However, It is of utmost importance to realize that BP and cardiovascular events have a continuous relation.[8] The cut-off values of hypertension are the levels of BP at which it was demonstrated that the benefits of treatment outweigh the risks of treatment.[9] In total, 76 patients had a systolic BP rise of ≥20 mmHg and/or a diastolic BP rise ≥10 mmHg at any time during the course of treatment with erenumab (52/109, 47.7%) or fremanezumab (24/87, 27.6%). Interestingly, after the first observed increase after three months of treatment, the mean systolic and diastolic BP remained stable. This might suggest that if a patient is at risk developing clinical relevant elevation of BP this will likely become apparent soon after initiating treatment. It is, however, worrisome that the rise in BP is a long lasting effect of treatment as we saw no signs of an adaptation process taking place within at least 12 months.

The exact mechanism underlying the increased risk of cerebro- and cardiovascular events in migraine patients is unknown, but underlying microvascular pathology and disturbance in endothelium function has been suggested.[10,11] It is unknown whether anti-CGRP (receptor) antibodies may enhance the increased cerebro/cardiovascular risk even further through the same mechanism. Importantly, physicians should be aware that migraine patients are at risk to develop hypertension when treated with anti-CGRP (receptor) antibodies and we strongly recommend that monitoring of BP should be added to (inter)national treatment guidelines on anti-CGRP treatment.

Part II Pathophysiological and clinical factors in relation to treatment efficacy

Peripheral versus central nervous system

Both the peripheral and central nervous system are involved in migraine, but, due to the multiple bidirectional interactions between these, there is

still some uncertainty on whether migraine is a disorder initiated in the central or peripheral nervous system. While premonitory symptoms are suggested to be related to hypothalamic reactivity, the aura has been associated with cortical spreading depolarization, and the headache phase has been associated with activation of the trigeminovascular system.[12,13]

Likewise, an ongoing debate exists as to whether photophobia, one of the most debilitating features of migraine, is a central or peripheral phenomenon in migraine. In migraine patients, there is evidence for hyperexcitability of the visual cortex, but also for different retinal rod responses to light compared to healthy controls.[14] However, the limitation of many studies investigating visual sensitivity in migraine, is that they focus solely on photophobia, while visual hypersensitivity in migraine patients actually comprises a broader concept. In addition to aversion for and pain from bright light, patients report aversion for and pain from flickering lights, patterns and certain colors. It has been argued that these last symptoms are most likely explained by cortical hyperexcitability, instead of retinal mechanisms.[14]

Migraine prophylactics all have different known sites of action, e.g. inhibition of betareceptors, inhibition of GABAergic activity, blocking the angiotensin II type 1 receptor, or blocking the CGRP-pathway, but it is unknown through which mechanism they prevent migraine, and whether this is a central or peripheral mechanism.[15] The monoclonal anti-CGRP (receptor) antibodies are designed to specifically block the ligand CGRP or its receptor and as the molecules are relatively large and are unlikely to pass the blood brain barrier, they most likely act peripherally, although passage through the blood brain barrier cannot completely be excluded.

In chapter 4 and 5 peripheral and central effects in relation to treatment with anti-CGRP (receptor) antibodies were investigated to gain insight in the mechanism and site of action of these prophylactic drugs. In **chapter 4** the relation between the trigeminovascular reactivity and the clinical response to treatment with erenumab was investigated. Capsaicin-induced dermal blood flow on the forehead was used to assess CGRP-mediated trigeminovascular activation before and after treatment initiation. Erenumab (partly) inhibited the capsaicin-induced trigeminovascular activity in all patients, regardless of the clinical effect, confirming a peripheral action. In **chapter 6,** visual hypersensitivity in migraine patients treated with erenumab and fremanezumab was described. Visual hypersensitivity

decreased after three months of treatment, with a clear positive association with the clinical response to treatment regarding migraine days. When separating the study population into patients with <50% and ≥50% reduction in MMD, only the ≥50% responders had a significant reduction in both *ictal* and *interictal* visual hypersensitivity.

The L-VISS questionnaire has been validated in migraine[16] and other chronic pain conditions[17] and both studies demonstrated results fitting central sensitization. While the visual hypersensitivity score did not decrease in <50% responders, we demonstrated in **chapter 4** that CGRP-mediated trigeminovascular activity is inhibited in patients with <50% response to treatment with erenumab. This suggests that visual hypersensitivity is not directly related to the peripheral blockade of the trigeminal nerve, and thus is likely a central phenomenon of migraine.

While we demonstrated that the L-VISS reduction after three months was correlated to the migraine reduction, it was suggested that early changes in laser evoked potentials are not correlated to clinical response.[18] However, these laser evoked potentials were measured after one week of treatment with erenumab and not repeated after three months. Thus, this does not contradict our statement that the decrease in visual hypersensitivity is likely secondary to the decrease in migraine days instead of a primary effect of treatment with anti-CGRP (receptor) antibodies.

(Non-)response to CGRP targeting treatment

Even though the anti-CGRP (receptor) antibodies are specifically developed for migraine, approximately half of patients do not have a relevant migraine reduction when treated with these drugs. In chapter 4 and 5 hypotheses on reasons for response were generated.In **chapter 4**, a lower CGRP-mediated trigeminovascular reactivity was found in patients with ≥50% response after 12 weeks of monthly 70 mg erenumab compared to patients with <50% response, both before and 2-4 weeks after initiation of the therapy. Additionally, the ≥50% responders had a significant reduction in both *ictal* and *interictal* visual hypersensitivity, while the L-VISS scores in the <50% responders did not change (**chapter 6**).

Considering that patients with <50% response had a higher trigeminovascular reactivity both before and after starting treatment with erenumab, it was hypothesized that for these patients erenumab 70 mg does not sufficiently

inhibit the CGRP-pathway and that these patients require a higher dose for preventive efficacy. Alternatively, low responders might require a different mechanism to block the CGRP-pathway. For instance, blocking the ligand CGRP (with eptinezumab, fremanezumab or galcanezumab) rather than the receptor (with erenumab). However, it is yet unknown whether an erenumab non-responder, might respond to one of these CGRP targeting antibodies, or vice versa. A third explanation for those patients with a low clinical response to anti-CGRP treatment might be involvement in these patients of non-CGRP-mediated pathways. Two other peptides that have been associated with both migraine and photophobia are amylin and pituitary adenylate cyclase activating polypeptide (PACAP).[19,20] Blockade of the amylin type 1 receptor (AMY1) receptor might be another mechanism to achieve improved efficacy in patients with inadequate response to CGRP targeting treatment that is yet to be investigated. PACAP antibodies are currently investigated as new migraine prophylactic treatment (NCT04197349). Further research is needed to assess whether patients with inadequate response to CGRP (receptor) blocking medication might respond to anti-PACAP or anti-amylin treatment. Finally, we obviously cannot exclude the importance of other, yet unidentified, mediators.

In **chapter 5** we investigated CGRP-LI levels before and shortly after (2-4 weeks) starting treatment with erenumab. We demonstrated that lower serum CGRP-LI levels measured shortly after starting treatment with erenumab are associated with the clinical response after three months, while this association was not found for serum CGRP-LI levels before start of treatment. This suggests that relevant changes in serum CGRP, promptly after starting anti-CGRP treatment, are important for clinical effectiveness. In contrast to the decrease we found in trigeminovascular reactivity (**chapter 4**), we could not demonstrate a similar decrease in serum CGRP-LI.

A lot is yet unknown about the effects of blocking the CGRP receptor. Indeed, it does not seem unlikely that serum levels of CGRP would increase due to upregulation after long term blockade of the CGRP receptor.[21,22] However, interactions between CGRP activity and several other peptides (and/or their receptors) probably induce a more complex cascade of events, that could either increase or decrease serum CGRP. CGRP can act through both the CGRP and the amylin 1 receptors, with unknown effects on further CGRP release.[23] In addition, CGRP release may be indirectly influenced by changing activity of the sympathetic nervous system and endogenous

endothelin-1 release, which may modulate CGRP release through the TRPV1 receptor.[24,25] Lastly, CGRP might regulate its own release through presynaptic mechanisms.[26]

Placebo response and CGRP-targeting treatment

As stated before, approximately 50% of migraine patients in clinical trials regarding anti-CGRP (receptor) antibodies had at least 50% reduction in MMD. In clinical trials including patients with previous failure to 2-4 migraine prophylactic treatments this was 30-40%, but, interestingly, this was also accompanied by a lower placebo response.[27-32] While in clinical trials the therapeutic gain compared to placebo is important, in clinical practice only the total response is relevant. In our own real world patient population, a population quite similar to the study population of these last trials, also approximately 30% of patients had ≥50% reduction in MMD (**chapter 2**).

Placebo response is the response that is seen after administration of a substance with no known therapeutic effect, that looks completely similar to a known treatment. Patients receiving a placebo usually don't know whether they receive the active or inactive (placebo) treatment. Interestingly, although placebo is often described as an inert substance, administration of a placebo leads to activation of several cortical areas, such as the anterior cingulate cortex and the dorsolateral prefrontal cortex.[33,34] Additionally, it is suggested that genetic factors are also of importance in placebo response.[35] Moreover, previous studies have demonstrated that social stimuli, such as words and rituals of the therapeutic act, drug administration route and patient expectations are important predictors of the outcome of both placebo and active analgesic treatments.[36,37] Thus, these factors might influence the treatment response to CGRP targeting treatment as well.

Even though we did not directly investigated it in regard to the CGRP-antibodies, the clinical trials as described above indicate that patients with more treatment failures experience both a lower placebo and a lower total response. It is imaginable that migraine patients, after having many unsuccessful treatments in the past, have lower expectations for a new treatment, and thus experience a lower treatment response. However, we cannot exclude the involvement of any other, perhaps disease-related, factors.

Part III Migraine and depression

In **chapter 7** we study depressive symptoms in relation to the clinical response to treatment with monoclonal anti-CGRP (receptor) antibodies. Erenumab and fremanezumab induced a reduction in depressive symptoms after 3 months of treatment, independent of migraine reduction. Furthermore, depressive symptoms before the start of treatment with erenumab was associated with poorer clinical response on MMD, while for fremanezumab we did not demonstrate this association.

Although it might be presumed that symptoms of depression will improve when patients experience less frequent migraine attacks, our study suggests that anti-CGRP treatment has an additional effect on reducing depressive symptoms. Interestingly, migraine and (major) depressive disorder have shared genetic factors[38,39] and both have been associated with higher levels of CGRP[38-42], thus, CGRP-blocking medication may influence both migraine and depressive symptoms independently. However, unlike in migraine the knowledge on involvement of CGRP in depressive symptomatology is limited. While the anti-CGRP (receptor) antibodies most likely act peripherally, mood disorders have been associated with changes in several brain areas.[43] If the antibodies would indeed modify depressive symptoms independent from decrease in migraine days, this would suggest that central actions may be modified by a peripheral effect. While erenumab (a CGRP receptor antibody) and fremanezumab (a CGRP antibody) affect the CGRP-pathway in a different way, by blocking the CGRP receptor or the CGRP peptide, respectively, we cannot conclude or proof for certain whether there is a difference between the two drugs in view of their action on depressive symptoms in migraine patients. More research is needed to further explore the relation between decrease in migraine and decrease in depressive symptoms in response to anti-CGRP treatment.

Migraine patients have an increased risk of developing a depression, with an even higher risk in patients with chronic migraine, and vice versa depression itself is a risk factor for chronification of migraine, which is accompanied by a higher disease burden and a lower quality of life.[44] Moreover, various prophylactic drugs used for preventive treatment in migraine are relatively contraindicated as they may increase the vulnerability for depression. Thus, physicians should be alert to symptoms of depression when they treat patients with migraine, also in patients with a relatively low frequency.

Interestingly, cognitive behavior therapy seems to increase the response to prophylactic migraine treatment,[45,46] but it is yet to be discovered whether simultaneous treatment of depression indeed will lead to a more successful reduction in monthly migraine days in patients treated with CGRP targeting treatment. Physicians should be aware of the negative influence of depression on treatment effectiveness and consider a multidisciplinary treatment approach.

After treatment of a migraine attack with triptans often patients still experience migraine symptomatology[47] and thus do not function optimally even though the headache has been resolved. Research focusing on the prediction of migraine attacks, might identify clinical or neurophysiological changes preceding a migraine attack, which may lead to treatment options disrupting a migraine attack in an earlier stage, further improving migraine care. In **chapter 8,** we evaluated whether symptoms of depression increase in the premonitory phase of a migraine attack in patients with episodic migraine. Even though in retrospective studies patients often report mood changes as a premonitory symptom, in our prospective diary study there was no increase in acute depressive symptoms observed in the days preceding the migraine headache. Migraine patients reported more acute depressive symptoms during their migraine headache day than on all other days of attack and after the headache day acute depressive symptoms normalized back to comparable levels as before. Migraine patients who fulfilled the criteria for lifetime depression, reported more acute depressive symptoms on every day of the migraine attack. Thus, acute depressive symptoms (especially mood changes and loss of interest) are not "early warning" signals that precede a migraine headache, but migraine patients do experience more acute depressive symptoms during a migraine headache, independent of life time depression. There is currently no evidence for an association between acute depressive symptoms during migraine and the risk for developing new onset of depression. However, as migraine patients do have an increased risk of developing a depression, with a risk for chronification[44], it is of utmost importance for physicians to be alert to depressive symptoms in patients with migraine. Especially since we demonstrated in **chapter 7** that the presence of depression might have a negative influence on treatment response.

Future perspectives

Major advancements in migraine care are needed. This is underlined by the fact that many migraine patients are left untreated after having failed

all current prophylactic treatment options, which has large socioeconomic consequences. Even so-called 'migraine specific' treatment options are not successful for every migraine patient. To improve migraine care, it is important to discover the mechanism of action of migraine treatment and reasons why patients do not respond to treatment.

Our research regarding the trigeminovascular system provides novel avenues for exploring reasons for why patients do or do not respond to anti-CGRP medication. Performing measurements of the trigeminovascular reactivity regarding an anti-CGRP antibody, such as fremanezumab or galcanezumab, is necessary to conclude whether the same effect will be observed in all CGRP targeting antibodies. Repeating the study with the longer existing preventive migraine drugs might provide evidence on whether these treatments also act through the trigeminovascular system. A study in healthy controls demonstrated a small reduction in capsaicin-induced trigeminovascular reactivity after administration of propranolol.[48] Additionally, the involvement of other vasoactive peptides needs to be explored. Not only CGRP, but also amylin, PACAP and adrenomedullin have been shown to be able to provoke migraine attacks in migraine patients.[19,20,49] While amylin and adrenomedullin can also act through the CGRP receptor, this is not the case for PACAP. It is important to gain understanding of how these and perhaps yet unidentified peptides are involved in migraine. Discovering whether they have a final common pathway or whether they lead to migraine through different pathways will be a major step in understanding migraine pathophysiology, which could lead to better treatment options.

Secondly, acquiring knowledge on the central and peripheral aspects of migraine, and research focusing on clinical and neurophysiological changes preceding a migraine attack will help to determine the site of origin of a migraine attack and thus could lead to establishing a new therapeutic site of action for future pharmacological treatments, both acute and prophylactic. In addition, more research regarding migraine and depressive symptomatology, may lead to a better understanding of the underlying (common) pathophysiology and perhaps will lead to the development of new treatment options for either or both diseases.

In this thesis we addressed one safety aspect of anti-CGRP (receptor) antibodies, namely the effect on the blood pressure. However, additional

knowledge is required regarding both the cardiovascular safety and the safety regarding pregnancy. In the (short-term) clinical trials no increased risk for cardiovascular events has been demonstrated. However, CGRP is suggested to play a protective role in case of ischemic events and seems to play a larger role in ischemic events in female patients than in male patients.[50] Specific safety studies, taking into account sex differences and predisposition for cardiovascular disease, and careful registration of side effects in real world situations will have to confirm the (long-term) safety. Regarding safety in pregnancy, less than 100 individual cases reported in the WHO pharmacovigilance database have yet been analysed.[51] No specific maternal toxicities, patterns of major birth defects, or increased reporting of spontaneous abortion were found. However, this is a very limited number of cases, thus registration of pregnancy outcomes and surveillance of lactating women needs to be continued urgently.

There are several studies that have identified differences between men and women with migraine. Both the prevalence and the symptoms reported differ between men and women. In addition, in healthy subjects it has been shown that plasma CGRP levels in women are significantly higher than in men, with even higher plasma CGRP found in women using combined hormonal contraceptives.[52] Interestingly, ovarian hormone receptors have been described in all the components of the trigeminovascular system and interactions between ovarian sex hormones and CGRP levels have been described.[53] The differences in plasma levels of CGRP between men and women, the changes in CGRP levels that occur in women in different life stages and the interaction between ovarian sex hormones and CGRP are yet to be studied as, perhaps, a partial explanation for the (non-)response to anti-CGRP treatment.

In conclusion, a better understanding of migraine pathophysiology, the site and mechanism of action of the current pharmacological migraine treatments and identifying patient-specific factors that predict the clinical response to treatment may ultimately lead to more personalized medicine for migraine.

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