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

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Chapter 10
Summary
Samenvatting

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This thesis describes the efficacy and safety of monoclonal antibodies directed against CGRP (fremanezumab) or the CGRP receptor (erenumab) as preventive treatment in migraine patients in a real world setting. Furthermore, it addresses factors that are predictive of the degree of the clinical response to this medication.

Part I contains the description of the clinical response to erenumab (**chapter 2**) and a safety analysis regarding blood pressure after starting treatment with erenumab or fremanezumab (**chapter 3**). Patients included in these studies all had high frequent episodic or chronic migraine and were highly treatment refractory, meaning that they previously failed on ≥ 4 prophylactic treatments. **Chapter 2** describes the monthly response to erenumab for a follow-up period of 6 months. A reduction in monthly migraine days, but not in non-migrainous headache days, was observed, along with a reduction in intake of acute medication, headache severity and accompanying symptoms, such as nausea, photophobia and phonophobia. There is a wide range in migraine reduction, and on individual level the response may not be consistent over a period of several months. Of all patients 36% experienced ≥50% monthly migraine days (MMD) reduction at least 3 out of 6 months, while only 6% of patients had ≥50% reduction all 6 months. For ≥30% MMD reduction a total of 60% of patients reached this level for half of the treatment period and 24% for all months. Of the patients with episodic migraine 26/54 (48%) had ≥50% reduction and 42/54 (78%) had ≥30% reduction at least 3 out of 6 months, for chronic migraine this was 10/46 (22%) and 18/46 patients (39%), respectively. It is proposed to consider these refractory patients who failed on ≥ 4 prophylactics a responder if there is ≥30% reduction in MMD for at least half of the treatment period.

In **Chapter 3** we evaluated the safety of the use of erenumab and fremanezumab regarding the blood pressure during a one year follow-up period. The mean systolic and diastolic blood pressure slightly increased after starting treatment with erenumab or fremanezumab. Fortunately, the majority of patients did not have a clinically relevant elevation in blood pressure, but four patients required treatment with antihypertensive drugs while having normal blood pressure before starting treatment. The subgroup analyses suggest a larger and more consistent rise in blood pressure in the erenumab subgroup than in the fremanezumab subgroup.

Physicians should be aware that migraine patients are at risk to develop hypertension when treated with anti-CGRP(receptor)antibodies and this should be added to (inter)national treatment guidelines.

In **part II** we investigated several factors as possible predictors for the clinical response to erenumab and fremanezumab. **Chapter 4** describes the trigeminovascular activity as a predictor for the clinical response to treatment with erenumab. The capsaicin-induced (CGRP-mediated) trigeminovascular activity reduces after treatment with erenumab is initiated. We found a lower trigeminovascular reactivity in patients with ≥50% response after 12 weeks of monthly treatment with 70 mg erenumab compared to patients with <50% response, both before and 2-4 weeks after initiation of the therapy. Based on these results, a few possible explanations are provided for non-responders to erenumab. Patients with insufficient reduction of migraine in response to erenumab may either need more effective CGRP receptor blockade (e.g. higher dosage), a different approach to block the CGRP pathway, or a treatment that targets a non-CGRP pathway.

Chapter 5 describes serum CGRP levels in relation to the clinical response to erenumab. Blood samples were collected before (T0) and 2-4 after (T1) starting treatment with erenumab. Lower serum CGRP shortly after starting treatment with erenumab was associated with a higher reduction in migraine days after three months of treatment. We did not find this association for baseline serum CGRP, nor could we demonstrate a significant decrease from T0 to T1. The association between CGRP at T1 and the clinical response suggests that changes in serum CGRP shortly after starting erenumab are important for clinical effectiveness.

In **Chapter 6** we describe visual hypersensitivity in migraine patients treated with erenumab or fremanezumab. The validated L-VISS questionnaire was used to assess visual sensitivity before starting treatment and after three months of treatment with either erenumab or fremanezumab. The visual sensitivity decreased, with a positive association between the clinical response and the reduction in visual hypersensitivity. When separating the group at a 50% response cut-off value, the ≥50% responders had a significant reduction in both *ictal* and *interictal* visual hypersensitivity, while the L-VISS scores in the patients with <50% reduction in migraine did not change. Furthermore, the degree of visual hypersensitivity in migraine patients before starting treatment does not seem to be a valuable predictor

for the clinical response to these antibodies. This may suggest that the decrease in visual hypersensitivity is secondary to the decrease in migraine frequency, due to a decrease in central sensitization.

Part III focuses on the relation of migraine and depression. **Chapter 7** describes research into depressive symptoms in relation to the clinical response to treatment with monoclonal anti-CGRP(receptor) antibodies. Treatment with monoclonal anti-CGRP (receptor) antibodies induced a reduction in depressive symptoms after 3 months of treatment. Importantly, this reduction in depressive symptoms was independent of the reduction in MMD. Furthermore, depressive symptoms before the start of treatment with erenumab were associated with poorer clinical response on monthly migraine days, while for fremanezumab we did not demonstrate this association. Physicians should be aware that anti-CGRP (receptor) antibodies lead to improvement of depressive symptoms, but at the same time be alert that depressive symptoms may be a negative predictor for migraine reduction.

Chapter 8 reports the temporal relationship between acute depressive symptoms before, during and after a migraine attack. Migraine patients reported more acute depressive symptoms during their migraine headache day than on all other days of the attack. No increase in acute depressive symptoms was observed in the days preceding the migraine headache 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.

Finally, **Chapter 9** provides a general discussion and suggests possibilities for future research.