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

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Part II
Pathophysiological and clinical factors in relation to treatment effectiveness

Chapter 4

CGRP-mediated trigeminovascular reactivity in migraine patients treated with erenumab

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Introduction

Migraine is a highly disabling disorder characterized by recurrent attacks of severe headache (https://ichd-3.org/). The trigeminovascular system and release of calcitonin gene-related peptide (CGRP), a neuromodulator and potent vasodilator, have a crucial role in the pathophysiology of migraine.[1] Monoclonal antibodies (mAbs) targeting CGRP (eptinezumab, fremanezumab, galcanezumab) or its receptor (erenumab) are novel prophylactics. Unfortunately, it is currently unknown which mechanisms are underlying the variability in response rates.

In addition to spontaneous release during migraine, CGRP can be released from trigeminal nerve endings by external stimuli. Application of capsaicin on the forehead releases CGRP via activation of the transient receptor potential cation channel subfamily V member 1 (TRPV1 channel) of the trigeminal nerve and thereby increases forehead dermal blood flow (DBF).[2] Forearm application of capsaicin also increases DBF and this effect can be inhibited by erenumab, but the dose-response relationship in this model does not seem to be indicative for clinical responses.[3]

We evaluated whether erenumab inhibits the forehead capsaicin-induced DBF response and whether the degree of capsaicin-induced DBF response before treatment is different in patients with an adequate versus suboptimal clinical response to erenumab.

Materials and Methods

Migraine patients were recruited from the Leiden Headache Centre. Patients were not using any other migraine prophylactics and had no medication overuse headache.

Approval was obtained from the Leiden University Medical Center Medical Ethical Committee and all participants gave written informed consent.

Clinical efficacy

A validated daily headache E-diary[4] was used to assess the occurrence and characteristics of headache and accompanying symptoms. The clinical response was assessed by comparing monthly migraine days (MMD) in week 9-12 (i.e. after three doses of erenumab) to that in the 4 weeks pretreatment baseline period. Participants were divided in those with a ≥50% MMD reduction compared to baseline (≥50% responders) and those with a <50% MMD reduction (<50% responders).

Trigeminovascular reactivity

A reservoir was placed on the forehead and after 15 minutes of supine rest, it was filled with capsaicin solution (6.0 mg/mL, dissolved in a mixture of ethanol 100%, Tween 20 and distilled water; 3:3:4). DBF was continuously measured for 40 min using a laser Doppler imager (PeriScan PIM (perfusion imager) 3 system, Perimed AB Sweden). The experiment was performed at baseline (T0), just before the first subcutaneous injection of erenumab 70 mg, and repeated 2-4 weeks (after T_{max}, but before the second dosing) after erenumab treatment was initiated (T1). Due to the high migraine frequency in our study population, the measurements could take place on a migraine or a non-migraine day.

Statistical analyses

Sample size calculations were based on previous studies using this model and took into account the expected group size differences based on response rate in clinical trials.[5] The area under the curve from 0–40 minutes, i.e. during the complete measurement (AUC_{0-40}) was used as primary outcome because this represents a composite measure for the response to capsaicin over time. For every participant, the AUC_{0-40} was calculated before (T0) and 2-4 weeks after (T1) starting erenumab. As DBF responses to capsaicin were not normally distributed, comparison between groups (i.e.

≥50% responders versus <50% responders) was made using Mann-Whitney U test. Comparisons between T0 and T1 were made using Wilcoxon-signed Rank test.

A two-sided p-value<0.05 was considered as significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA)

Results

Participants

In total, 49 patients were invited for this study and all agreed to participate. One participant was not able to attend the second study visit because of a debilitating migraine attack and was excluded from all analyses. There were 13 ≥50% responders (12 women) with a mean age of 45 years and 12.5 MMDs at baseline. Twelve of these patients had episodic migraine, 9 had migraine without aura, and 10 fulfilled the criteria for allodynia. In the <50% responders group, there were 35 patients (26 women), with a mean age of 40 years and 14.4 MMDs at baseline. Fourteen of these patients had episodic migraine, 22 had migraine without aura, and 27 fulfilled the criteria for allodynia. The disease duration was very similar between groups: 23 years (range 10 - 41) for the ≥50% responders, and 24 (range 5 - 47) years for the <50% responders.

DBF response to capsaicin

T1 took place after a median of 14 days (range 14-25). The AUC_{040} was smaller in ≥50% compared to <50% responders, both at T0 (U=139, p=0.04) and at T1 (U=129, p=0.02) (Figure 1). The AUC_{040} decreased after erenumab was started, both in the ≥50% responders (Z=-3.180, p<0.001) and in the <50% responders (Z=-5.159, p<0.001) (Figure 1).

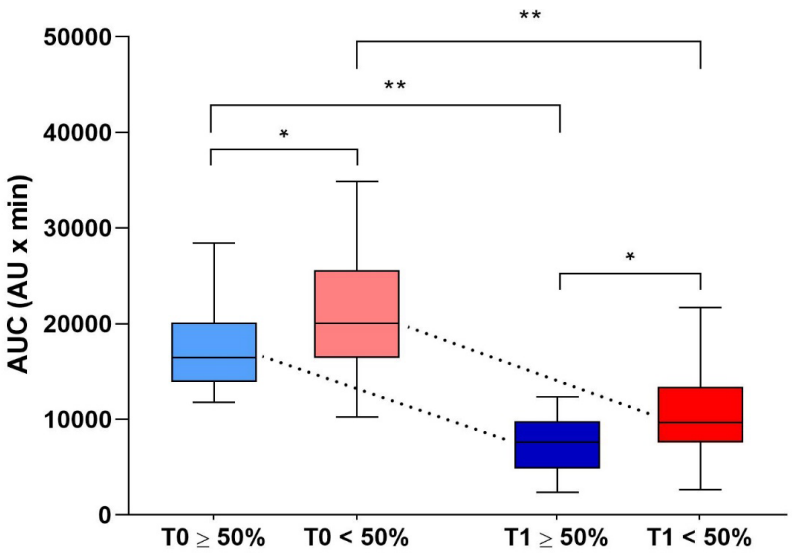

Figure 1 $AUC_{0\text{-}40}$ of DBF response to capsaicin 6.0 mg/mL in participants with <50% and ≥50% response to erenumab at T0 and T1. Boxplot whiskers represent minimum and maximum values of data. T0 = before starting treatment with erenumab, T1 = 2-4 weeks after first erenumab injection. ≥50% = patients with ≥50% reduction in migraine days after three months of treatment with erenumab(n = 13), <50% = patients with <50% reduction in migraine days after three months of treatment with erenumab (n = 35). DBF = dermal blood flow. AU = arbitrary units. * $p < 0.05$. ** $p < 0.001$.

Discussion

We used capsaicin-induced DBF on the forehead to assess CGRP-mediated trigeminovascular activation before and after erenumab treatment. Erenumab (partly) inhibited capsaicin-induced trigeminovascular activity in all patients, regardless of the clinical effect. Trigeminovascular reactivity was higher in patients with <50% response compared with patients with ≥50% response, both before and 2-4 weeks after initiation of the therapy. Therefore, we hypothesize that in <50% response patients erenumab 70 mg did not sufficiently inhibit the CGRP pathway, possibly due to a higher initial activity of the trigeminovascular system. This suggests that <50% responders would require a higher dose for preventive efficacy.

Another explanation may be a more important role for alternative mechanisms in blocking the CGRP pathway, such as blocking the CGRP ligand rather than the receptor. However, it is yet unknown whether a

non-responder to erenumab might respond to one of the CGRP-binding antibodies. Alternatively, CGRP might induce part of its effect via different receptors, such as the amylin type 1 receptor.

A third explanation for a low clinical response to erenumab might be involvement of non-CGRP-mediated pathways, for example, via the pituitary adenylate cyclase-activating peptide (PACAP) pathway, but obviously further research is needed to assess whether patients with inadequate response to CGRP-targeting medication might benefit from anti-PACAP treatment. Finally, we obviously cannot exclude the involvement of other, yet unidentified, mediators.

A strong feature of our study is the use of a time-locked electronic headache diary. Data were prospectively collected and the short delay for completing a specific diary day avoids recollection bias. In this study, only one third of patients were ≥50% responders, which is similar to that in the erenumab trial, in which patients were included who had failed on two to four prophylactics.[5]

Because of the high attack frequency, study visits could not always be scheduled on interictal days. Measurements on ictal days were, however, not different from those on interictal days.

In conclusion, this study indicates a relation between trigeminovascular activity and the treatment response to erenumab. It provides a potential biological mechanism for the difference in clinical response between patients, and, thus, opens novel avenues for further research aimed at improving and understanding the response to CGRP-inhibiting medication.

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