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

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Chapter 6

Visual hypersensitivity in migraine patients treated with monoclonal anti-CGRP (receptor) antibodies

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Submitted

Abstract

Objective To evaluate the effect of treatment with anti-CGRP (receptor) antibodies on visual hypersensitivity in migraine patients.

Background Increased visual sensitivity can be present both during and outside of migraine attacks. CGRP has been demonstrated to play a key role in light aversive behavior.

Methods In this prospective follow-up study, patients treated for migraine with erenumab (n=105) or fremanezumab (n=100) in the Leiden Headache Center were invited to complete a questionnaire on visual sensitivity (L-VISS), pertaining to both their *ictal* and *interictal* state, before starting treatment (T0) and 3 months after treatment initiation (T1). Using a daily e-diary, treatment effectiveness was assessed in week 9-12 compared to a 4 week pre-treatment baseline period. L-VISS scores were compared between T0 and T1. Subsequently, the association between reduction in L-VISS scores and the reduction in monthly migraine days (MMD) was investigated

Results At three months, the visual hypersensitivity decreased, with a decrease in *ictal L-VISS* (from 20.1 ± 7.7 to 19.2 ± 8.1, p = 0.042) and a borderline significant decrease in *interictal L-VISS* (from 11.8 ± 6.6 to 11.1 ± 7.0, p = 0.050). We found a positive association between the reduction in MMD and the decrease in interictal L-VISS (β = 0.2, p = 0.010) and the reduction in ictal L=VISS (β = 0.3, p = 0.001).

Conclusion Decrease in visual hypersensitivity in migraine patients after treatment with anti-CGRP (receptor) antibodies is positively associated with clinical response on migraine.

Introduction

Migraine is a debilitating disorder characterized by recurrent headaches, accompanied by photo- and phonophobia and/or severe nausea or vomiting.[1] The trigeminovascular system and calcitonin-gene related peptide (CGRP) have a crucial role in the pathophysiology of migraine. CGRP levels are elevated during spontaneous migraine attacks and infusion of this peptide induces migraine-like headache in migraine patients.[2, 3] These findings have led to the development of three monoclonal antibodies directed against the ligand CGRP (eptinezumab, fremanezumab and galcanezumab) and one directed against the CGRP receptor (erenumab). In clinical trials, it was shown that treatment with CGRP (receptor) antibodies leads to more patients with a 50% reduction in monthly migraine days (generally considered a relevant treatment response[4]) in comparison to placebo.[5] When patients are studied in whom 2-4 migraine prophylactics had failed or who suffer from chronic migraine the success rate is lower.[6, 7] Unfortunately, no patient-specific response predictive factors so far have been identified.

Migraine headaches are accompanied by altered sensory perception[8], typically causing patients to avoid any type of sensory stimulation, e.g. light, sound, touch or smell. Because increased visual sensitivity can be present both during and outside of attacks[9, 10], it greatly contributes to the overall burden of migraine. However, the exact pathophysiological mechanism is unknown. Currently there is an ongoing debate on whether the origin is localized peripherally or centrally.[11]

In mouse models, CGRP has been demonstrated to play a key role in light aversive behavior.[8] This was first observed in CGRP sensitized mice, with an overexpressed RAMP1 subunit of the CGRP receptor, but also in wild-type mice. Pre-treatment with a CGRP-blocking antibody attenuated this behaviour.[12]

In this study we hypothesized that treatment with anti-CGRP (receptor) antibodies diminishes visual hypersensitivity in migraine patients. In addition, we evaluated whether the change in visual hypersensitivity is dependent on migraine reduction and whether interictal visual hypersensitivity is a predictor for the clinical response to this treatment.

Methods

Participants

All patients who started treatment with erenumab or fremanezumab in the Leiden Headache Center, a national referral center in the Netherlands, were invited to participate in this prospective follow-up study. All patients were diagnosed with migraine according to the International Classification of Headache Disorders third edition (ICHD-3)[1] by a headache specialist. None of the patients had a second primary headache disorder, other than tension type headache. Following a strict policy in the Netherlands regarding starting new treatment with anti-CGRP mAbs, none of the patients had medication overuse (as defined by the ICHD-3[1]), or was treated with concomitant prophylactic migraine drugs. All patients had ≥8 migraine days per month and failed on ≥4 migraine prophylactics (i.e. ineffective, discontinued because of side effects or being contraindicated), including a betablocker, candesartan, valproate and topiramate.

Treatment

All patients were treated with either erenumab (70 mg) or fremanezumab (225 mg), administered subcutaneously, once every four weeks. No dose adjustments were made in the study period. As described above, no additional prophylactic treatment was used.

Headache diary

To assess the clinical treatment response, all patients completed a validated daily e-diary.[13] This diary contains questions on headache presence, headache characteristics, accompanying symptoms and the use of pain medication. When a headache was present, an automated algorithm following on the ICHD-3 criteria determined whether it was a migraine day. Additionally, a day on which a triptan was taken and the occurrence of an aura were also counted as migraine days. Patients started the diary at least 4 weeks before treatment with erenumab or fremanezumab was started (the baseline period). Clinical response to treatment was assessed in the third month (week 9-12) after initiating treatment. One month is defined as 28 days (4 weeks).

Leiden Visual Sensitivity Scale

The Leiden Visual Sensitivity Scale (L-VISS) is a questionnaire developed to quantify self-reported visual sensitivity to light and patterns and

was previously validated in migraine patients.[14] It contains nine items, all answered on a 5-point Likert scale (0-4, total range 0-36). Patients completed the questionnaire both regarding symptoms during migraine attacks (*ictal* L-VISS), and regarding symptoms outside of migraine attacks (*interictal* L-VISS). Patients were invited to complete the questionnaire at baseline (T0) and after three months of treatment with either erenumab or fremanezumab (T1).

Depression

To assess symptoms of depression, the Hospital Anxiety and Depression Scale (HADS)[15] and Center for Epidemiological Studies Depression Scale (CES-D)[16] questionnaires were used. Both questionnaires focus on symptoms experienced in the previous week and were filled out at baseline (T0). As a measurement of current indication of depression, we defined 'active depression' as a HADS-D score ≥ 8 and/or CES-D ≥ 16, comparable to previous studies.[17, 18]

Statistical analyses

Sample size was based on the available data. No statistical power calculation was conducted prior to the study. Baseline characteristics, including, sex, age, headache diagnosis, number of failed prophylactics and baseline headache measures were summarized using means and standard deviations or frequencies and proportions. Failure to the prophylactics propranolol and metoprolol was counted as one failure (treatment class: betablockers).In line with clinical trials[7], for each patient the clinical response to treatment with erenumab or fremanezumab was determined by calculating the absolute reduction in monthly migraine days (MMD) in the third month (week 9-12) after initiating treatment compared to the baseline month (4 weeks before starting treatment). The relative MMD reduction was calculated in order to divide the patient population into patients with ≥50% MMD reduction and <50% MMD reduction.

Pre-post treatment comparisons

Our primary outcome was the comparison of L-VISS scores between T0 and T1. As L-VISS scores were normally distributed, we compared the L-VISS scores using paired samples t-tests. The secondary outcome was the association between migraine reduction and reduction in L-VISS scores, which was analyzed in two different ways. Firstly, we made two simple linear regression models with MMD reduction as independent variable;

one with reduction in interictal L-VISS score, and one with reduction in ictal L-VISS score as dependent variable. Secondly, we divided the participants in patients with ≥50% and <50% MMD reduction, and repeated the paired samples t-tests between T0 and T1.

Response predictor

As an exploratory analysis, visual hypersensitivity was assessed as a predictor for the clinical response to treatment with erenumab and fremanezumab. Simple linear regression models were used to test associations, with the absolute reduction in MMD in the third month after treatment initiation as the dependent variable and the *interictal* L-VISS score, age, gender, migraine days at baseline, migraine with vs migraine without aura and active depression as predictor variables. We reran the analysis as a multiple regression model, adjusting for the potential confounding effects of all variables that were tested. We were specifically interested in the interictal visual hypersensitivity and left out ictal L-VISS scores, as these two are strongly correlated.

In all analyses, patients treated with erenumab and fremanezumab were analyzed together. For all analyses, two-tailed p-values < 0.05 were considered as statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

Missing data

No imputation methods were used for missing questionnaires. Missing diary days were not imputed, as the average diary compliance was high.

Standard protocol Approvals, Registration and Patient Consents

This study was approved by the Medical Ethics Committee of the Leiden University Medical Center and all patients were asked to provide written informed consent.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Baseline characteristics

A total of 218 patients starting treatment with erenumab or fremanezumab were invited to participate. Of these patients, 205 patients completed the three month follow-up period and the questionnaires at baseline (erenumab n = 105, fremanezumab n = 100) and 189 (erenumab n = 99, fremanezumab n = 90) also completed the questionnaires after 3 months follow-up. The majority of patients were female (85% in the erenumab group, 82% in the fremanezumab group). In both groups approximately 60% of patients had migraine without aura. Patients starting treatment with fremanezumab were more often diagnosed with chronic migraine (59%) compared to patients starting treatment with erenumab (49%). Diary compliance was 97%. Baseline characteristics are described in table 1.

Table 1 Patient baseline characteristics.

	Erenumab (n = 105)	**Fremanezumab (n = 100)**
Female, n (%)	89 (85)	82 (82)
Age, mean ± SD	43 ± 12	44 ± 13
Migraine without aura, n (%)	64 (61)	62 (62)
Chronic migraine, n (%)	51 (49)	59 (59)
MMD baseline, mean ± SD	14 ± 5.6	15 ± 6.5
MHD baseline, mean ± SD	17 ± 6.3	18 ± 6.9
MAMD baseline, mean ± SD	6 ± 3.6	5 ± 2.8
Failed prophylactics, mean ± SD	5 ± 1.0	5 ± 1.1

MMD = monthly migraine days. MHD = monthly headache days. MAMD = Monthly acute medication days.

Pre-post treatment comparisons

Patients with complete data on both timepoints (baseline and 3 month follow-up) were included in these analyses (n = 189).

Both mean *ictal* and *interictal* L-VISS scores of the total population slightly decreased after three months of treatment compared to baseline (Figure 1). The mean ± SD *ictal* L-VISS score decreased from 20.1 ± 7.7 to 19.2 ± 8.1 (p = 0.042). The mean *interictal* L-VISS score decreased from 11.8 ± 6.6 to 11.1 ± 7.0, but this was marginally significant (p = 0.050).

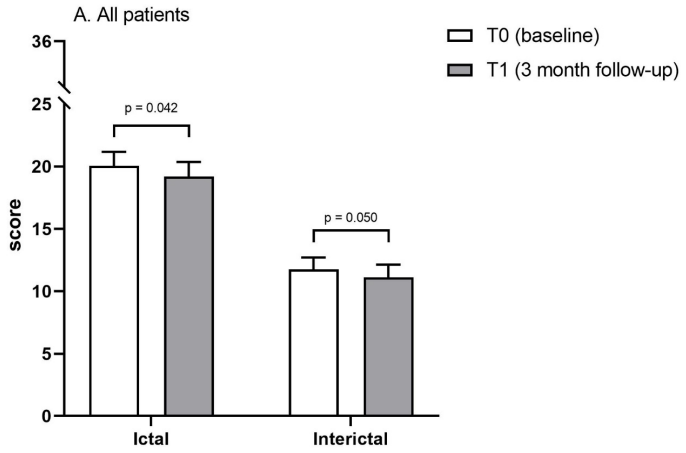

Figure 1 L-VISS score before (T0) and 3 months after (T1) starting treatment with erenumab or fremanezumab. All patients (n = 189). Data presented as mean ± 95% confidence interval. L-VISS = Leiden Visual Sensitivity Scale (total range 0-36).

We found a positive association between the reduction in MMD and the decrease in interictal L-VISS (β (95% CI) = 0.2 (0.0 - 0.3), p = 0.010) and the reduction in ictal L-VISS (β (95% CI) = 0.3 (0.1 – 0.5), p = 0.001).

In patients with ≥50% reduction in MMD (n = 63) the mean *ictal* L-VISS decreased from 19.0 ± 8.2 to 16.5 ± 9.4 (p = 0.002) (Figure 2). The mean *interictal* L-VISS decreased from 10.1 ± 6.4 to 8.8 ± 6.6 (p = 0.021). In contrast, in patients with <50% reduction in MMD (n = 126) the mean *ictal* L-VISS did not change, baseline 20.6 ± 7.4 vs three months follow-up 20.5 ± 7.1 (p = 0.911). The mean *interictal* L-VISS did not change either, after mean ± SD: 12.6 ± 6.6 after three months compared to baseline mean ± SEM: 12.3 ± 6.9 (p = 0.482) (Figure 2).

Results for episodic and chronic migraine patients separately are presented in supplementary table 1.

Response predictor

Table 2 presents the unadjusted β-coefficients (left column) and adjusted β-coefficients (right column) and p-values of the linear regression analyses. Absolute reduction in MMD in response to treatment with erenumab and fremanezumab seemed not associated with *interictal* L-VISS (p = 0.069).

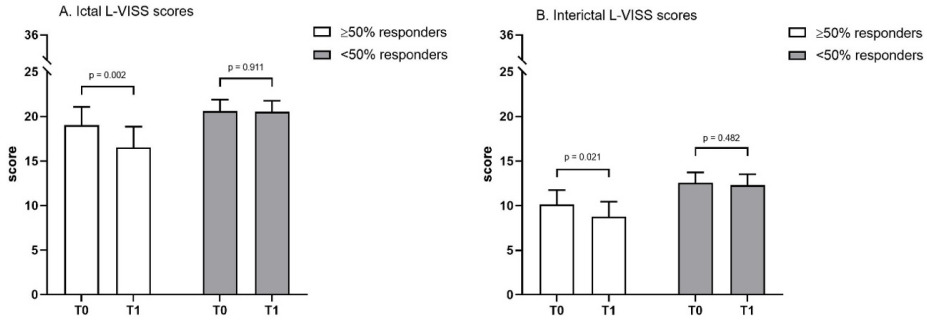

Figure 2 L-VISS scores before (T0) and 3 months after (T1) starting treatment with erenumab or fremanezumab separately for <50% and ≥50% responders. Data presented as mean ± 95% confidence interval. L-VISS = Leiden Visual Sensitivity Scale (total range 0-36). <50% responders = patients with <50% reduction in migraine days after three months of treatment with erenumab (n = 126). ≥50% responders = patients with ≥50% reduction in migraine days after three months of treatment (n = 63).

Table 2 linear regression analysis.

Variable	β (95% CI)[1]	p	β (95% CI)[2]	p
Age	0.0 (-0.0 - 0.1)	0.154	0.1 (0.1 - 0.1)	**0.027**
Gender	1.6 (-0.2 - 3.4)	0.083	2.0 (0.3 - 3.8)	**0.021**
Migraine days baseline	0.2 (0.1 - 0.3)	**0.001**	0.2 (0.1 - 0.3)	**<0.001**
MA or MO	0.6 (-0.8 – 2.0)	0.394	0.6 (-0.8 – 2.0)	0.399
Active depression	-0.5 (-1.9 - 0.9)	0.473	-0.6 (-2.0 - 0.8)	0.389
L-VISS interictal baseline	-0.1 (-0.2 - 0.0)	0.256	-0.1 (-0.2 - 0.0)	0.069

N = 205. [1]Simple linear regression. [2]multiple regression, corrected for all tested variables. CI = confidence interval. L-VISS = Leiden Visual Sensitivity Scale (total range 0-36). Active depression = HADS-D ≥ 8 and/or CES-D ≥ 16. Gender: 0 = male. MO = migraine without aura, MA = migraine with aura. MA = 0. Outcome = absolute reduction migraine days month 3 after starting treatment with erenumab or fremanezumab compared to baseline. One months is defined as 28 days.

Discussion

In this observational study we evaluated whether treatment with monoclonal anti-CGRP (receptor) antibodies attenuated visual hypersensitivity in migraine patients as measured with the L-VISS questionnaire. Visual hypersensitivity decreased after three months of treatment, with a clear association with clinical response to treatment regarding migraine days.

The degree of visual hypersensitivity before starting treatment was not a predictor for clinical response to these antibodies.

The L-VISS scores in our study are comparable to the values previously found in the validation study of the L-VISS questionnaire.[14] These findings are well in line with previous findings on CGRP-mediated light aversive behavior in animal models.[12] Additionally, in a clinical trial with telcagepant, a small molecule CGRP receptor antagonist for the acute treatment of migraine, patients reported less photophobia after treatment.[19] Likewise, in clinical trials[20, 21] and a real-world study[22] with anti-CGRP (receptor) antibodies also less ictal photophobia was reported after treatment. However, in these studies only overall group results were described and the association with reduction in monthly migraine days was not analyzed.

Up to 90% of migraine patients report photophobia during a migraine headache (ictal)[9] and about 60% report it outside of migraine attacks (interictal).[10] There is evidence for both a central (e.g. hyperexcitability of the visual cortex)[6, 23] and a peripheral (e.g. differences in retinal rod responses)[24, 25] origin for photophobia. The limitation of many studies researching visual sensitivity in migraine is that they focus solely on photophobia. However, visual hypersensitivity in migraine patients comprises a much 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.[11] It has been reasoned that these last symptoms are most likely explained by cortical hyperexcitability and thus indicative for central origin.[11] Noteworthy, the attenuation of light aversion in the animal study was demonstrated in relation to peripherally administered CGRP.[12] This supports the suggestion that peripherally administered CGRP causes photophobia by a mechanism that is different from visual hypersensitivity phenomena that are more certain to be of central origin.[12]

The L-VISS questionnaire has been validated in migraine[14] and other chronic pain conditions[26] and was shown to be indicative for central sensitization. While the visual hypersensitivity score in the present study did not decrease in patients with <50% MMD reduction in response to treatment with erenumab, in a different study we demonstrated that the CGRP-mediated trigeminovascular activity is inhibited in these <50% responders.[27] This suggests that the decrease in visual hypersensitivity is not directly related to trigeminal nerve blockage, but may be a secondary effect of decrease in

migraine days. This would fit the data that monoclonal antibodies targeting CGRP are large molecules that can hardly pass the blood brain barrier, and most likely work via a peripheral site of action.

A reduction in migraine frequency in response to treatment with CGRP-targeting treatment might lead to a reversal of central sensitization. Frequent migraine attacks can, by recurrent activity of the trigeminal neurons, lead to a process of augmentation of pain by mechanisms of the central nervous system. Projections from cortical regions, thalamus and hypothalamus to brainstem sites form a descending pain modulatory system.[28] This process of central sensitization has been associated with the progression of episodic migraine to chronic migraine.[29] Although the exact time span needed for central sensitization to be reversed is not known, it might fit our time-frame with the clinical response to treatment with anti-CGRP (receptor) antibodies and the decrease in visual hypersensitivity. Altered sensory perception in migraine patients has been associated with enhanced CGRP activity[8] and therefore visual hypersensitivity has previously been suggested to be potentially predictive of the response to CGRP-blocking treatment.[14] Being able to predict in advance which patient will be good responders to treatment will be a major advancement in migraine care. Unfortunately, we could not identify the L-VISS questionnaire as a predictor for the response to treatment with erenumab or fremanezumab in our patient population.

Two other peptides that have been associated with migraine and photophobia are amylin and pituitary adenylate cyclase activating polypeptide (PACAP).[30, 31] The stable amylin analogue pramlintide induced migraine-like attacks in patients with migraine without aura, most likely through the amylin type 1 receptor.[30] In addition, light aversive behavior was observed in mice after administration of amylin.[30] Infusion of PACAP can induce migraine-like headache and photophobia in migraine patients.[31] Antibodies directed against PACAP inhibit PACAP-induced light aversive behavior in mice.[32] PACAP antibodies are currently investigated as new migraine prophylactic treatment (NCT04197349*).*

A strong feature of the present study is the use of a validated e-diary. The collection of detailed daily headache characteristics enables a reliable assessment of monthly migraine days and the time-lock prevents reporting bias. In addition, we used a validated questionnaire, with a good to excellent internal consistency and test–retest reliability to asses visual hypersensitivity

in migraine patients. Furthermore, none of the participants used any other prophylactic migraine treatment, excluding the influence of (perhaps centrally acting) prophylactic drugs on visual hypersensitivity. For example, topiramate modulates excitability of the occipital cortex.[33] A limitation of our study design is that we can only speculate if the reduction in L-VISS scores is indeed mediated by the reduction in migraine days. Our results need to be replicated in future studies. Secondly, patients were treated with erenumab 70 mg. We cannot be certain about additional effects of erenumab 140 mg. Thirdly, our follow-up is relatively short. A longer follow-up period would demonstrate whether the decrease in visual hypersensitivity is a long lasting effect or whether there is a lag in improvement. Lastly, our analysis with the *interictal* L-VISS as a predictor for response needs to be interpreted with caution. Gender seemed to have a significant effect, however, we need to take into account that there were very few men in our analyses and our study was not powered for this analysis. Whether there is indeed a difference in effectiveness of monoclonal CGRP-antibodies between men and women needs to be investigated in a separate study. In addition, it would be interesting to investigate whether erenumab and fremanezumab might have a different effect on visual sensitivity. Unfortunately, in the current study there is not enough power to make a comparison. Although the response rate in our patient population is similar to that in the clinical trials in which patients were included who failed on two to four prophylactics[6, 7], the number of responders is relatively low, causing insufficient statistical power for more subgroup analyses.

Visual hypersensitivity is one of the most debilitating features of migraine. Even if the migraine headache is successfully treated, many migraine patients still report this as one of the most bothersome associated migraine symptoms.[34] Even though we found a significant decrease in visual hypersensitivity, this reduction was relatively small and dependent on the reduction in migraine. When considering previously reported L-VISS scores in migraine patients and healthy controls[14], it is not expected that visual hypersensitivity resolves completely, even when patients convert from chronic migraine to episodic migraine. However, as photophobia is one of the most bothersome symptoms of a migraine attack, every decrease could already be relevant in the total burden experienced during a migraine attack. A more extensive understanding of this phenomenon will help to improve the understanding of the pathophysiology of migraine in general and treatments targeting this associated phenomenon will be a major advancement in the treatment of migraine.

Conclusion

Visual hypersensitivity in migraine patients diminished after treatment with CGRP (receptor) targeting treatment. This reduction was positively associated with the monthly migraine day reduction in response to this treatment. We hypothesize that the reduction in visual sensitivity is most likely secondary to the decrease in migraine frequency, due to a reversal of central sensitization, and not a primary effect of preventive CGRP-targeting treatment.

Highlights

- Visual hypersensitivity is a debilitating feature of migraine which can be both present during and outside of attacks.
- Visual hypersensitivity diminishes in response to treatment with monoclonal anti-CGRP (receptor) antibodies.
- We hypothesize that the reduction in visual sensitivity is secondary to the decrease in migraine days, due to reversal of central sensitization, and not a primary effect of CGRP-targeting treatment.

Supplementary Table 1 L-VISS score comparisons between baseline vs 3 month follow-up for episodic and chronic migraine patients.

	Episodic migraine				**Chronic migraine**			
		Baseline	**3 months**	**p-value***		**Baseline**	**3 months**	**p-value***
All patients	N = 91				N = 98			
	L-VISS ictal	18.9 ± 0.8	17.73 ± 0.9	0.08	**L-VISS ictal**	21.2 ± 0.8	20.6 ± 0.8	0.27
	L-VISS interictal	10.5 ± 0.7	10.18 ± 0.7	0.42	**L-VISS interictal**	12.9 ± 0.7	12.0 ± 0.7	0.07
< 50% responders	N = 51				N = 75			
	L-VISS ictal	19.5 ± 1.0	19.5 ± 1.1	0.93	**L-VISS ictal**	21.4 ± 0.9	21.2 ± 0.8	0.84
	L-VISS interictal	11.6 ± 0.9	11.4 ± 0.9	0.75	**L-VISS interictal**	13.2 ± 0.8	12.9 ± 0.8	0.53
≥ 50% responders	N = 40				N = 23			
	L-VISS ictal	18.1 ± 1.3	15.5 ± 1.4	**0.02**	**L-VISS ictal**	20.6 ± 1.8	18.3 ± 2.1	**0.05**
	L-VISS interictal	9.1 ± 1.0	8.6 ± 1.1	0.38	**L-VISS interictal**	12.0 ± 1.3	9.1 ± 1.4	**0.03**

Data presented in mean ± SEM. L-VISS = Leiden Visual Sensitivity Scale (score range 0-36); <50% responders = patients with <50% reduction in migraine days after three months of treatment with erenumab. ≥50% responders = patients with ≥50% reduction in migraine days after three months of treatment. *paired samples t-test.

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