Visual hypersensitivity in patients treated with anti-calcitonin gene-related peptide (receptor) monoclonal antibodies

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RESEARCH SUBMISSIONS

Visual hypersensitivity in patients treated with anti-calcitonin gene–related peptide (receptor) monoclonal antibodies

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Abstract

Objective: To evaluate the effect of treatment with anti-calcitonin gene–related peptide (CGRP; receptor) antibodies on visual hypersensitivity in patients with migraine.

Background: Increased visual sensitivity can be present both during and outside 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 (the Leiden Visual Sensitivity Scale [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 weeks 9–12 compared to a 4-week pre-treatment baseline period. L-VISS scores were compared between T0 and T1. Subsequently, the association between the reduction in L-VISS scores and the reduction in monthly migraine days (MMD) was investigated.

Results: At 3 months, the visual hypersensitivity decreased, with a decrease in mean ± standard deviation (SD) ictal L-VISS (from 20.1 ± 7.7 to 19.2 ± 8.1, $p=0.042$) and a decrease in mean ± SD 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 ($\beta=0.2$, $p=0.010$) and the reduction in ictal L-VISS ($\beta=0.3$, $p=0.001$).

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

KEYWORDS
central sensitization, erenumab, fremanezumab, migraine, visual hypersensitivity

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scale; CGRP, calcitonin gene–related peptide; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; ICHD-3, International Classification of Headache Disorders, 3rd edition; L-VISS, Leiden Visual Sensitivity Scale; mAbs, monoclonal antibodies; MMD, monthly migraine days; PACAP, pituitary adenylate cyclase activating polypeptide; SD, standard deviation.

Antoinette MaassenVanDenBrink and Gisela M. Terwindt are shared last authors.

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 patients with migraine.[2,3] These findings have led to the development of three monoclonal antibodies (mAbs) directed against the ligand CGRP (eptinezumab, fremanezumab, and galcanezumab) and one directed against the CGRP receptor (erenumab). In clinical trials, it has been shown that treatment with CGRP (receptor) antibodies leads to more patients with a 50% reduction in monthly migraine days (MMD; generally considered a relevant treatment response[4]) compared to placebo.[5] When patients for whom two to four migraine prophylactics had failed or who suffer from chronic migraine were studied, the success rate was 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, including 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 regarding 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 receptor activity modifying protein 1 subunit of the CGRP receptor, but also in wild-type mice. Pre-treatment with a CGRP-blocking antibody attenuated this behavior.[12]

In this study we hypothesized that treatment with anti-CGRP (receptor) antibodies will diminish visual hypersensitivity in patients with migraine. In addition, we evaluated whether the change in visual hypersensitivity was 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, 3rd 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 beta-blocker, candesartan, valproate, and topiramate.

Treatment

All patients were treated with either erenumab (70 mg) or fremanezumab (225 mg), administered subcutaneously, once every 4 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 contained questions on headache presence, headache characteristics, accompanying symptoms, and the use of pain medication. When a headache was present, an automated algorithm following the ICHD-3 criteria determined whether it was a migraine day. Additionally, days on which a triptan was taken and a reported 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 (weeks 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 patients with migraine.[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 3 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 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 (SDs) or frequencies and proportions. Failure of the prophylactics propranolol and metoprolol was counted as one failure (treatment class: beta-blockers). 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 MMD in the third month (weeks 9–12) after initiating treatment compared to the baseline month (4 weeks before starting treatment). The relative MMD reduction was calculated 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. First, we made two simple linear regression models with MMD reduction as an independent variable; one with reduction in interictal L-VISS score, and one with reduction in ictal L-VISS score as the dependent variable. Second, we divided the 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, sex, migraine days at baseline, migraine with versus 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 statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp.).

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.

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 3-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 of follow-up. Most 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. The included and

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

Abbreviations: MAMD, monthly acute medication days; MHD, monthly headache days; MMD, monthly migraine days; SD, standard deviation.

excluded patients were comparable regarding age, sex, MMD, and treatment response.

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 3 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 ($p=0.050$).

We found a positive association between the reduction in MMD and the decrease in interictal L-VISS (β [95% confidence interval (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 versus 3-month 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 3 months compared to baseline mean ± standard error of the mean: 12.3 ± 6.9 ($p=0.482$; Figure 2).

Results for patients with episodic and chronic migraine separately are presented in Table S1 in supporting information.

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 ($p=0.069$).

DISCUSSION

In this observational study we evaluated whether treatment with monoclonal anti-CGRP (receptor) antibodies attenuated visual hypersensitivity in patients with migraine as measured with the L-VISS questionnaire. Visual hypersensitivity decreased after 3 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 (ictal L-VISS 19.7 ± 7.2, interictal L-VISS 9.9 ± 5.7).[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 MMD was not analyzed.

Up to 90% of patients with migraine 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 (i.e., hyperexcitability of the visual cortex)[6,23] and a peripheral (i.e., 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;

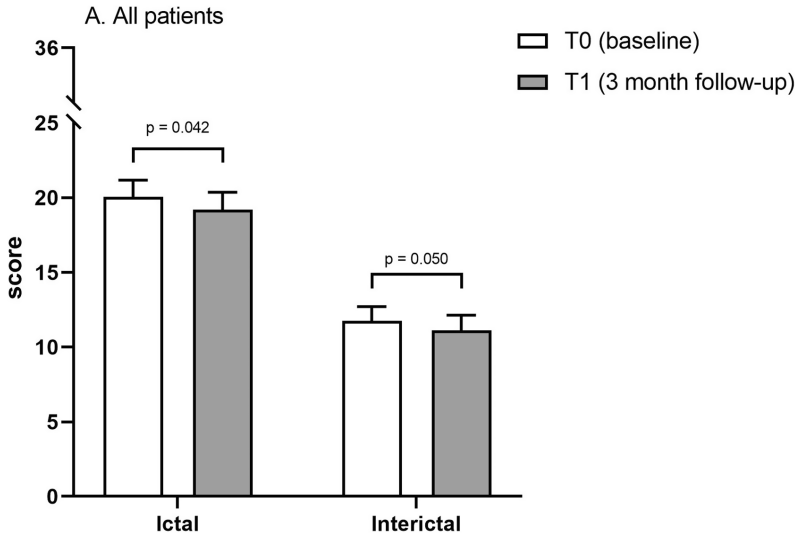

FIGURE 1 Leiden Visual Sensitivity Scale (L-VISS) score before (T0) and 3 months after (T1) starting treatment with erenumab or fremanezumab. All patients ($n=189$). Data presented as mean ± 95% confidence interval. L-VISS (total range 0–36).

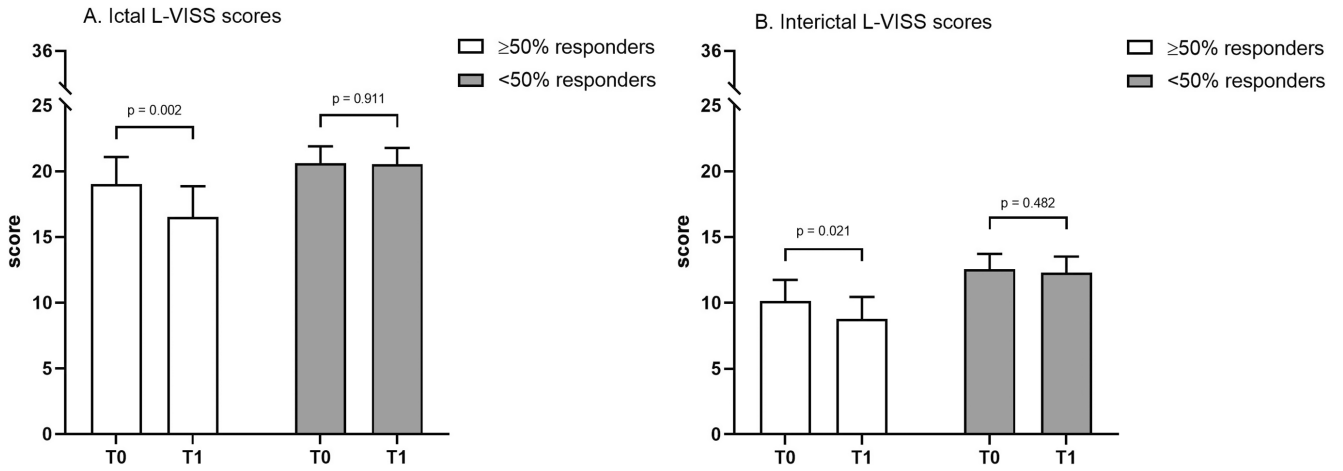

FIGURE 2 Leiden Visual Sensitivity Scale (L-VISS) scores before (T0) and 3 months after (T1) starting treatment with erenumab or fremanezumab separately for <50% and ≥50% responders. Data presented as mean ± 95% confidence interval. L-VISS (total range 0–36). <50% responders = patients with <50% reduction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

TABLE 2 Linear regression analysis.

Variable	β (95% CI)[a]	p	β (95% CI)[b]	p
Age	0.0 (−0.0–0.1)	0.154	0.1 (0.1–0.1)	**0.027**
Sex	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

Note: $N = 205$. Active depression = HADS ≥8 and/or CES-D ≥16. Sex: 0 = male. MWA = 0. Outcome = absolute reduction migraine days month 3 after starting treatment with erenumab or fremanezumab compared to baseline. One month is defined as 28 days. Values in bold are statistically significant.

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scale; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; L-VISS, Leiden Visual Sensitivity Scale (total range 0–36); MA, migraine with aura; MO, migraine without aura.

[a]Simple linear regression.

[b]Multiple regression, corrected for all tested variables.

however, visual hypersensitivity in patients with migraine 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 latter symptoms are most likely explained by cortical hyperexcitability and thus indicative of a central origin.[11] It is noteworthy that 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 of 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 mAbs targeting CGRP are large molecules that cannot easily 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 patients with migraine 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 patients 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. Increasing the research population might lead to a significant outcome as the power increases; however, even if this is the case, the effect probably remains small. The current found beta = −0.1, meaning that an increase of 10 points on the L-VISS scale leads to 1 day less migraine reduction.

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 patients with migraine.[31] Antibodies directed against PACAP inhibit PACAP-induced light-aversive behavior in mice.[32] PACAP antibodies are currently being investigated as a 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 MMD 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 assess visual hypersensitivity in patients with migraine. 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. Second, patients were treated with erenumab 70 mg. We cannot be certain about additional effects of erenumab 140 mg. Third, our follow-up was 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. Last, our analysis with the interictal L-VISS as a predictor for response needs to be interpreted with caution. Sex 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 different effects 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 patients with migraine still report this as one of the most bothersome symptoms associated with migraine.[34] Even though we found a significant decrease in visual hypersensitivity, this reduction was relatively small and dependent on the reduction in migraine. Considering previously reported L-VISS scores in patients with migraine 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 patients with migraine diminished after treatment with CGRP (receptor) targeting treatment. This reduction was positively associated with the MMD 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.

AUTHOR CONTRIBUTIONS

Study concept and design: Simone de Vries Lentsch, Johannes A. Carpay, Antoinette MaassenVanDenBrink, Gisela M. Terwindt. *Acquisition of data*: Simone de Vries Lentsch. *Analysis and interpretation of data*: Simone de Vries Lentsch, Matthijs J. L. Perenboom, Johannes A. Carpay, Antoinette MaassenVanDenBrink, Gisela M. Terwindt. *Drafting of the manuscript*: Simone de Vries Lentsch. *Revising it for intellectual content*: Simone de Vries Lentsch, Matthijs J. L. Perenboom, Johannes A. Carpay, Antoinette MaassenVanDenBrink, Gisela M. Terwindt. *Final approval of the completed manuscript*: Simone de Vries Lentsch, Matthijs J. L. Perenboom, Johannes A. Carpay, Antoinette MaassenVanDenBrink, Gisela M. Terwindt.

CONFLICT OF INTEREST STATEMENT

Gisela M. Terwindt reports consultancy support from Novartis, Allergan, Lilly, Teva, and Lundbeck, and independent support from Dutch Research Council, the Dutch Heart & Brain Foundations,

IRRF, and Dioraphte. **Antoinette MaassenVanDenBrink** reports consultancy or industry support from Novartis, Lilly, and Teva, and independent support from the Dutch Research Council and the Dutch Heart & Brain Foundations. **Johannes A. Carpay** reports consultancy support from Novartis, Allergan, Lilly, Lundbeck, and Teva. **Simone de Vries Lentsch** declares no conflicts of interest. **Matthijs J. L. Perenboom** declares no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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