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SHORT COMMUNICATION

Both perimenstrual and nonperimenstrual migraine days respond to anti-calcitonin gene-related peptide (receptor) antibodies

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Abstract

Background and purpose: Anti-calcitonin gene-related peptide (CGRP) (receptor) antibodies effectively reduce overall migraine attack frequency, but whether there are differences in effect between perimenstrual and nonperimenstrual migraine days has not been investigated.

Methods: We performed a single-arm study among women with migraine. Participants were followed with electronic E-diaries during one (pretreatment) baseline month and 6 months of treatment with either erenumab or fremanezumab. Differences in treatment effect on perimenstrual and nonperimenstrual migraine days were assessed using a mixed effects logistic regression model, with migraine day as dependent variable; treatment, menstrual window, and an interaction term (treatment × menstrual window) as fixed effects; and patient as a random effect.

Results: There was no interaction between the menstrual window and treatment effect, indicating that the reduction in migraine days under treatment was similar during the menstrual window and the remainder of the menstrual cycle (odds ratio for treatment = 0.44, 95% confidence interval = 0.38–0.51).

Conclusions: Our findings support prophylactic use of anti-CGRP (receptor) antibodies for women with menstrual migraine, as this leads to consistent reductions in number of migraine days during the entire menstrual cycle.

KEYWORDS
CGRP, erenumab, fremanezumab, menstrual migraine, migraine

INTRODUCTION

Migraine is a brain disorder predominantly affecting women. Migraine headache arises from activation of the trigeminovascular system and subsequent release of calcitonin gene-related peptide (CGRP) [1]. New prophylactic antimigraine drugs target CGRP or its receptor.

Migraine symptoms in women are more refractory, in particular during menstruation and the menopausal transition phase [2, 3]. Sex hormone receptors are coexpressed with CGRP and CGRP receptors in all components of the trigeminovascular system and may thus affect the trigeminovascular system directly [4]. Estrogen in particular is often hypothesized to increase susceptibility to migraine attacks

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[4, 5]. Perimenstrual migraine attacks are usually attributed to the sudden drop in estrogen levels prior to menstruation [6]. CGRP plasma levels have been related to estrogen levels, in both animal and human studies [4]. In individuals without headache, plasma CGRP levels were shown to be significantly higher in women than in men, with even higher levels in women using hormonal contraception and lower levels in postmenopausal women [7].

Anti-CGRP (receptor) monoclonal antibodies (mAbs) reduce migraine frequency in both men and women, including women with menstrual migraine. Whether there are differences in response between perimenstrual and nonperimenstrual migraine days is unknown [8, 9]. We primarily compared the effect of anti-CGRP (receptor) mAbs on perimenstrual versus nonperimenstrual migraine days in women with migraine. In an additional exploratory analysis, we compared overall response in women and men.

METHODS

This was a post hoc analysis from a single-arm study on the efficacy of erenumab [10] and fremanezumab in a real-world setting. The study was approved by the medical ethics committee of the Leiden University Medical Center. All patients provided written informed consent.

Patients with migraine from the Leiden Headache Center who had ≥8 monthly migraine days (MMD) and had failed (ineffective treatment, side effects, or contraindication) on at least candesartan, a beta blocker, valproate, and topiramate were eligible for treatment with erenumab or fremanezumab. Diagnosis was based on the International Classification of Headache Disorders (ICHD)-3 and was made by a neurology resident in consultation with a headache neurologist [11]. Exclusion criteria were a second primary headache diagnosis, other than occasional tension type headache, medication overuse headache, or a history of cerebrovascular or cardiovascular events. Prophylactic medication was tapered off before baseline, including a washout period. Patients treated with erenumab started with 70 mg once every 4 weeks. After 3 months, dosage was optionally increased to 140 mg, based on shared decision-making. Patients treated with fremanezumab were treated with 225 mg once every 4 weeks.

Patients completed a validated headache E-diary during at least one baseline and six treatment months (defined as 28 days) [2]. E-diary adherence had to be ≥80%. Data on headache, medication use, and menstruation were collected. Migraine days were defined with an ICHD-3-derived algorithm based on migraine-specific characteristics or aura symptoms or triptan intake. Migraine days occurring during the 5-day menstrual window were considered perimenstrual migraine days [11]. All other migraine days were defined as nonperimenstrual.

For the primary analysis, only women were selected. As not all women menstruated on a regular basis (e.g., continuous hormonal contraception or menopause), analyses regarding the menstrual cycle were performed in a subset of women who registered ≥3 menstruations. No distinction was made between menstrual migraine and nonmenstrual migraine on a patient level.

For each woman, the total number of MMD, perimenstrual migraine days, and nonperimenstrual migraine days was calculated for baseline and each treatment month. In addition, the percentage of women with a migraine day on each day of the menstrual cycle was calculated. Menstrual cycles were standardized to 28 days; the perimenstrual days of the menstrual cycle were fixed to 5 days, and the nonperimenstrual days were standardized to 23 (28 − 5) days. For MMD calculations, empty entries were considered headache-free.

Differences in treatment effect on perimenstrual and nonperimenstrual migraine days were assessed using a mixed effects logistic regression model, with migraine day as dependent variable; treatment, menstrual window, and an interaction term (treatment × menstrual window) as fixed effects; and patient as a random effect. The interaction term indicates whether there are differences in treatment effect on perimenstrual and nonperimenstrual migraine days on a multiplicative scale. Sensitivity analyses with missing nonperimenstrual days imputed as headache-free and missing perimenstrual days as migraine, and vice versa, were performed.

Exploratory analyses were performed to compare overall treatment effect in men versus women with migraine day as dependent variable; treatment, sex, and an interaction term (treatment × sex) as fixed effects; and patient as a random effect.

Two-sided p-values <0.05 were considered significant. Analyses were performed in R V3.6.1.

RESULTS

A total of 187 patients were treated with either erenumab or fremanezumab in the course of 6 months. Thirteen patients were excluded due to insufficient E-diary compliance, yielding 174 included patients (Table 1).

Analyses on perimenstrual versus nonperimenstrual migraine days were performed in 45 menstruating women. Median cycle length was 28.1 (Q1–Q3 = 26.8–31.2) days in women with a natural menstrual cycle ($n=34$) and 36.8 (Q1–Q3 = 32.2–70.8) days in women using hormonal contraceptives ($n=11$). In Figure 1a, the observed percentage of women with a migraine day is presented for each day of the menstrual cycle during baseline and follow-up. Relative reduction in total MMD between baseline (1 month) and follow-up (6 months) was 31.4% (4.4 ± 3.7 days), which comprised a reduction of 28.4% (0.7 ± 1.6 days) in perimenstrual migraine days and 32.1% (3.7 ± 3.9 days) in nonperimenstrual migraine days (Figure 1b).

There was no interaction between the menstrual window and treatment effect ($\beta=0.07$, 95% confidence interval [CI] = −0.30 to 0.43, $p=0.726$), indicating that the reduction in migraine days under treatment was similar during the menstrual window and the remainder of the menstrual cycle (odds ratio [OR] for treatment = 0.44, 95% CI = 0.38–0.51). Sensitivity analyses assuming that missing nonperimenstrual days were headache-free and missing perimenstrual days were migraine days, and vice versa, showed similar results.

TABLE 1 Baseline characteristics presented by sex.

Characteristic	Women with ≥3 menstrual cycles, primary analysis	Women	Men
Patients, *n*	45	144	30
Age, years	37.4 ± 10.2	45.0 ± 12.6	45.2 ± 11.5
Migraine with aura	16 (35.5)	45 (31.2)	6 (20.0)
MMD baseline	12.0 [10.0; 17.0]	12.0 [10.0; 17.0]	11.0 [9.0; 15.8]
MHD baseline	16.0 [11.0; 22.0]	16.0 [12.0; 22.0]	16.0 [12.0; 20.8]
Chronic migraine	18 (40.0)	55 (38.2)	11 (36.7)
Hormonal contraceptive use	11 (24.4)	57 (39.6)	NA
Menstrual cycles, *n*	7 [5; 7]	0 [0.0; 5.0]	NA
Treated with erenumab	28 (62.2)	85 (59.0)	20 (56.6)
Switch to 140 mg[a]	13 (46.4)	51 (60.0)	10 (50.0)
Treated with fremanezumab	17 (37.8)	59 (41.0)	13 (43.3)
E-diary compliance, %	98 [97; 100]	99 [97; 100]	99 [97; 100]

Note: Data are shown as either mean ± SD, median [Q1; Q3], or *n* (%). Chronic migraine was defined according to ICHD-3 criteria as ≥15 headache days, of which ≥8 were migraine days.

Abbreviations: MHD, monthly headache days; MMD, monthly migraine days; NA, not applicable.

[a]Percentages were calculated for patients treated with erenumab.

Next, we evaluated whether the reduction in MMD under treatment differed between men ($n = 30$) and women ($n = 144$). There was a significant interaction effect between sex and treatment, suggesting that treatment effect was greater for women compared to men (OR females = 0.41, 95% CI = 0.38–0.44; OR males = 0.57, 95% CI = 0.48–0.68; $p < 0.001$). The course of mean MMD during the entire follow-up is presented by sex in Figure 1c.

DISCUSSION

Similar relative reductions in perimenstrual and nonperimenstrual migraine days were found in women treated with anti-CGRP (receptor) mAbs. Migraine predominantly affects women of reproductive age, in whom fluctuations in sex hormone levels are suggested to increase attack susceptibility. Perimenstrual migraine attacks are longer, and more likely to recur after effective treatment with a triptan [12]. Women often need to take triptans repeatedly during perimenstrual attacks, and adequate prophylactic treatment is often necessary to avoid medication overuse. Therefore, it is encouraging that our findings show equal effectiveness of anti-CGRP (receptor) mAbs for both perimenstrual and nonperimenstrual migraine days.

A post hoc analysis from a randomized controlled trial also showed overall efficacy of erenumab in women with self-reported menstrual migraine [8]. However, no distinction was made between perimenstrual and nonperimenstrual migraine days. In addition, a case series described a higher perimenstrual migraine risk in both erenumab responders and nonresponders, but the sample size was small and no comparisons were made with the pretreatment situation [13]. Differences in responsiveness to prophylactic therapy between perimenstrual and nonperimenstrual attacks have otherwise only been investigated for topiramate, which showed equal reductions [14].

We found suggestive evidence for a possible sex difference in effect of anti-CGRP (receptor) mAbs in favor of women. However, due to the small sample size and nonrandomized, nonblinded nature of this study, results should be interpreted cautiously. Researchers should present clinical trial data by sex and age, as there is an urgent need for meta-analyses assessing sex differences in the effect of anti-CGRP (receptor) mAbs. Sex differences in response to migraine drugs have been described for acute treatment with triptans and were carefully suggested for prophylactic treatment with onabotulinumtoxinA [3, 15].

Our study has several strengths. We used data from a single-arm study in a well-defined migraine population [10]. Treatment with erenumab and fremanezumab was in the context of a single-arm study, setting high standards for inclusion of patients and collection of baseline and follow-up data. Data were collected with our previously validated E-diary, which defines individual migraine days according to an ICHD-3-based algorithm [2]. In addition, day-to-day data on menstruation were collected, which enabled us to reliably distinguish perimenstrual from nonperimenstrual days. The E-diary was time-locked, reducing the risk of recall bias. In general, compliance with the E-diary was high. Only few patients had to be excluded due to insufficient data. A mixed model accounting for missing migraine information showed similar results as sensitivity analyses in which either missing perimenstrual days were imputed as headache-free and nonperimenstrual days as migraine day, or vice versa, indicating that missing data had a negligible influence on our results.

A limitation of this study might be that due to the restricted availability of anti-CGRP (receptor) mAbs, the included population consisted of high-frequency migraine patients, which might result in regression

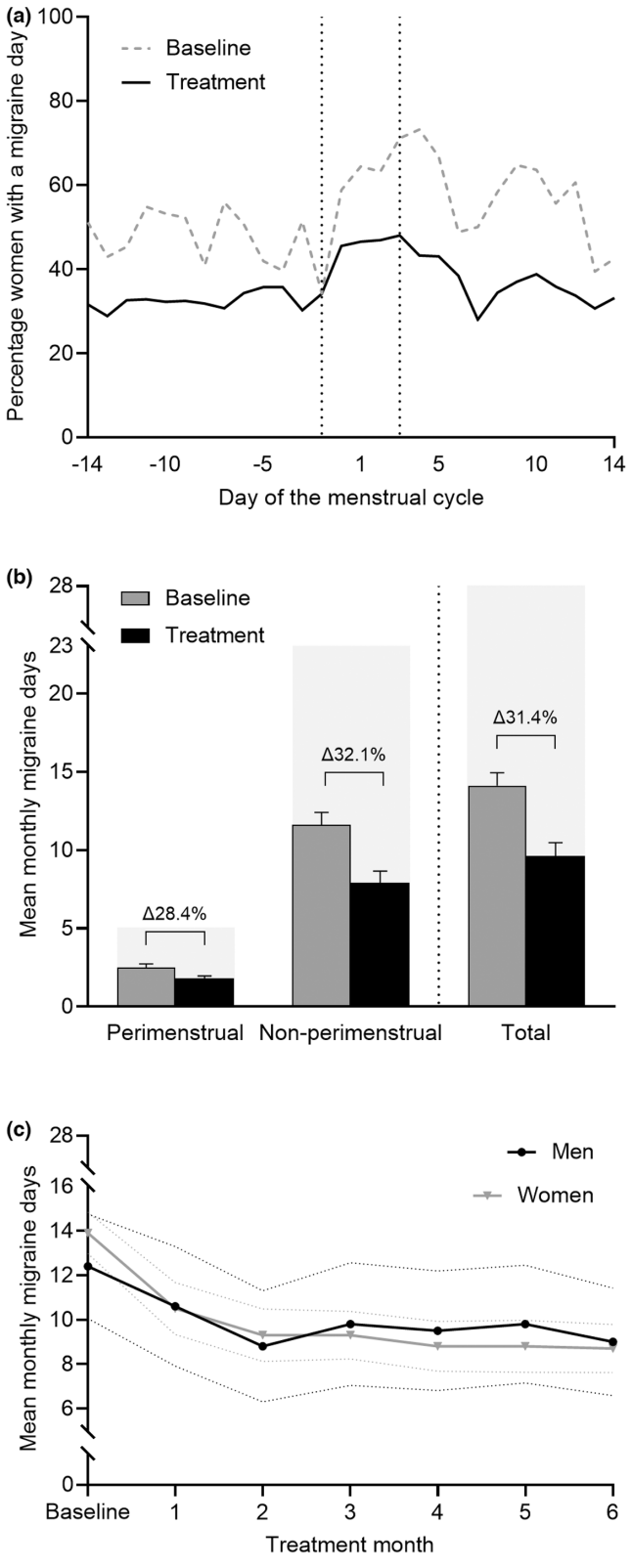

FIGURE 1 (a) Percentage of women with a migraine day for each day of the menstrual cycle during baseline (1 month before treatment) and follow-up (6 months of treatment). Data from 271 menstrual cycles from 45 menstruating women are shown. Menstrual cycles were standardized to 28 days; the perimenstrual days of the menstrual cycle were fixed to 5 days, and the nonperimenstrual days were standardized to 23 (28 – 5) days. (b) Number of mean monthly migraine days ± SE during baseline and follow-up for menstruating women ($n = 45$). The shaded area shows the theoretical number of perimenstrual and nonperimenstrual days. (c) Course of mean monthly migraine days with 95% confidence intervals during baseline and 6 months of follow-up.

to the mean. However, this does not compromise the interpretation of differences between subgroups and perimenstrual and nonperimenstrual migraine days. Furthermore, we pooled erenumab and fremanezumab data, as stratification would lead to small sample sizes. The effect of mAbs targeting CGRP might differ from those targeting the receptor. However, evaluating the crude data for erenumab and fremanezumab separately showed no indications for contradictory results (data not shown). Finally, the included population consisted of chronic and high-frequency episodic migraine patients, which made identifying individual migraine attacks difficult. We analyzed treatment effect on perimenstrual and nonperimenstrual migraine days in the total cohort of menstruating women, as migraine days are also the recommended primary outcome according to the International Headache Society clinical trial guidelines for preventive treatments [16].

Our findings support prophylactic use of anti-CGRP (receptor) antibodies for women with menstrual migraine, as this leads to consistent reductions in number of migraine days during the entire menstrual cycle.

AUTHOR CONTRIBUTIONS

All authors contributed to conception and design of the study. Iris E. Verhagen, Simone de Vries Lentsch, Britt W. H. van der Arend, and Saskia le Cessie contributed to acquisition and analysis of data. Iris E. Verhagen and Simone de Vries Lentsch contributed to drafting a significant portion of the manuscript or figure.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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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