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

S. de Vries Lentsch

Part III
Migraine and depression

Chapter 7

Depression and treatment with anti-CGRP (receptor) antibodies for migraine

Simone de Vries Lentsch[1*], Britt W.H. van der Arend[1,2*], Irene de Boer[1], Erik van Zwet[3], Antoinette MaassenVanDenBrink[2#], Gisela M. Terwindt[1#]

[1]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

[2]Division of Vascular Medicine and Pharmacology, Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

[3]Department of Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands

*These authors contributed equally to this study

#These authors contributed equally to this study

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Abstract

Objective To evaluate the effect of anti-CGRP (receptor) antibodies on depressive symptoms in subjects with migraine, and to analyze whether depression is a predictor of response to treatment with these drugs.

Methods We invited all people with migraine treated with erenumab and fremanezumab at the Leiden Headache Center to complete a daily e-headache diary. We also included a control group. Questionnaires on depressive symptoms (HADS, CES-D) were sent before they started treatment (T0) and after three months (T1). HADS-D ≥8 and/or CES-D ≥16 was labelled as 'active depression'. The proportions of participants with active depression were compared between T0 and T1, using a McNemar test. To assess the effect of treatment on the reduction in HADS-D and CES-D scores, independent of migraine reduction, a multiple linear regression model was used with reduction in depression scores as the dependent variable and reduction in monthly migraine days (MMD) and treatment with anti-CGRP medication as independent variables. To investigate depression as a predictor for clinical response, a multiple linear regression model was used, with absolute reduction in MMD as a dependent variable and age, gender, MMD, active depression, impact, stress, locus of control scores (all at baseline) as independent variables.

Results In total, n=108 patients were treated with erenumab, n=90 with fremanezumab, and n=68 without active treatment. Both HADS-D and CES-D scores decreased after three months of treatment with CGRP (receptor) antibodies ($p<0.001$), but not in the control group ($p=0.16$). There was a reduction in proportion of people with active depression for erenumab (70% to 47%, $p<0.001$) and fremanezumab (59% to 32%, $p<0.001$), but not for controls (66% to 63%, $p=0.839$). Treatment with anti-CGRP medication was associated with a reduction in HADS-D ($\beta = 2.45$, $p<0.001$) and CES-D ($\beta= 4.30$, $p=0.001$), independent of MMD reduction. Active depression was associated with poorer response to erenumab ($p=0.05$) but not to fremanezumab ($p=0.13$).

Conclusion Anti-CGRP (receptor) monoclonals lead to improvement of depressive symptoms in participants with migraine, independent of migraine reduction. We found a negative association between active depression before starting treatment with erenumab, but not with fremanezumab, and the clinical response.

Introduction

New preventive treatment options for migraine targeting the CGRP pathway are available; three monoclonal antibodies targeting the CGRP ligand (eptinezumab, fremanezumab and galcanezumab), and one monoclonal antibody targeting the CGRP receptor (erenumab). As a thumb rule for clinical practice, preventive migraine treatment in general may lead to approximately 50% reduction in monthly migraine days (MMD) in half of individuals. The other half does not reach 50% reduction in migraine and often starts a long search for an effective preventive treatment. This process is often based on trial and error, as it is currently not possible to predict which patients will respond to which specific drugs.

Persons with migraine are at increased risk of depression, and shared genetic factors may underlie this association.[1-3] Comorbid depression in individuals with migraine is an important predictor for acute medication overuse, and associated with an increased risk of chronification.[4-6] In this triad, there is a role for cutaneous allodynia and the underlying mechanism central sensitization.[7-9] Depression has been associated with poorer response to acute treatment and preventive treatment with onabotulinumtoxin-A.[10,11] For the new anti-CGRP (receptor) antibodies it is unknown whether depression, independently of number of migraine days, influences the treatment response. Furthermore, whether these antibodies improve symptoms of depression (in)dependently of the treatment response is also yet to be discovered.

In this study we aimed: i) to assess whether treatment with erenumab or fremanezumab improves comorbid depressive symptoms, (in)dependent of reduction in MMD; ii) to evaluate whether depressive symptoms, and other psychological traits, are predictive of response to preventive treatment with anti-CGRP (receptor) antibodies. Increasing the understanding of treatment response and identifying determinants for response may provide an advancement in migraine treatment.

Methods

Literature search

An extensive literature search (PubMed, Embase) up to august 2022 was performed to find all evidence regarding depression and monoclonal anti-CGRP (receptor) antibodies. Two researchers independently evaluated the articles based on abstract and if available the whole article (SdVL and BvdA). In case of a disagreement a discussion took place. The selection of the relevant articles and abstracts are presented in a table.

Participants

We included participants that started treatment with erenumab or fremanezumab at the Leiden Headache Center of the Leiden University Medical Center (LUMC), and a control group who was assessed in the same manner. They were diagnosed with migraine with or without aura by a neurologist with headache expertise according to the ICHD-3 criteria.[12] Migraine frequency had to be at least 6 migraine days per month. None of the subjects had a second primary headache disorder other than tension type headache, which is common in patients with chronic migraine.[12] If patients switched between different anti-CGRP treatments, only the data of the first treatment were included. As a control group we included people with migraine of the Leiden Headache Center with similar distribution in gender, age and migraine diagnosis and frequency. We used 2:1 matching on baseline active depression in which a single untreated participant was randomly matched to two treated participants. The control group received no active treatment in a blinded randomized fashion as part of other concurring investigator-initiated studies, and otherwise met the same criteria as the erenumab and fremanezumab group regarding failure on previous preventive treatments.

Treatment

Participants were treated with erenumab (70 mg) or fremanezumab (225 mg), administered subcutaneously, once every four weeks. No additional preventive treatment was used.

Headache diary

For all participants, including the control group, the clinical response was monitored using a daily headache e-diary, validated in the Leiden Headache Center.[13] This e-diary contains questions on the presence of

headache, headache characteristics, accompanying symptoms and the use of acutely acting migraine medication. When a headache is present, an automated algorithm based on the ICHD-3 criteria determines whether it is a migraine day. Additionally, days in which a triptan is taken, or days with the occurrence of an aura (with or without headache symptoms), are also counted as migraine days. Patients started this diary at least four weeks before starting treatment (baseline period). Clinical response was based on the reduction in migraine days in the third month after initiating treatment. A month is defined as 28 days (4 weeks).

Questionnaires

At (T0) and after three months (T1), all participants were invited to complete several questionnaires, which are described below.

Depression questionnaires

Patients filled out the Hospital Anxiety and Depression Scale (HADS) and the Center for Epidemiological Studies Depression Scale (CES-D). The HADS is a 14-item questionnaire, of which 7 items focus on symptoms of anxiety (HADS-A) and 7 items focus on symptoms of depression (HADS-D).[14] All items are answered on a 4-point Likert scale, ranging from 0 till 3 (both total scores ranging from 0 – 21). On each of these subscales a score of ≥ 8 is indicative of respectively a possible anxiety or a possible depressive disorder. The CES-D is a 20-item questionnaire, score ranging from 0-60.[15] All items are answered on a 4-point Likert scale, from 0 (rarely or none of the time) till 3 (most or all of the time). A score of ≥16 is indicative of possible depressive disorder. Both questionnaires focus on symptoms experienced in the previous week and were completed at baseline (T0) and after three months of treatment (T1). We defined 'active depression' as a HADS-D score ≥ 8 and/or CES-D ≥ 16, comparable to previous studies.[1,16]

Headache Impact Test-6

HIT-6 is a 6-item questionnaire that assesses the impact headache has a on a patient's daily life.[17] Every item is answered by a 5-point Likert scale ranging from never (score 6) till always (score 13), comprising a total score between 36 and 78, with larger scores reflecting a higher impact. This questionnaire was completed at baseline (T0) and after three months of treatment (T1).

Perceived stress scale

The perceived stress scale (PSS) is a measure of the degree to which situations are appraised as stressful.[18] This questionnaire consists of 10 questions, with every item scored on a 5-point Likert scale ranging from 0 (never) till 4 (very often). It focuses on feelings and thoughts experienced in the last month. A higher score correlates with more perceived stress. This questionnaire was completed at baseline (T0).

Headache specific Locus of Control

The headache specific locus of control (HSLC) assesses the individual's perceptions that headache problems and relief are determined by internal factors, health care professionals, or chance factors.[19] It consists of 33 statements, answered on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Every subscale (internal, health care professionals, chance) of the HSLC consists of 11 questions (scores range 11-55). A higher score on each different subscale means higher beliefs in that subscale of the locus of control. This questionnaire was completed at baseline (T0).

Statistical analyses

Baseline characteristics

Baseline characteristics were summarized using means and standard deviations or frequencies and proportions. Failure to the preventives propranolol and metoprolol was counted as one failure (treatment class: betablockers). Baseline scores of the different questionnaires (HIT-6, PSS, HADS, CES-D, HSLC) were summarized as means and standard deviations. For each patient, the clinical response was determined by calculating both the absolute and relative reduction in migraine days in the third month (week 9-12) compared to the baseline month (4 weeks before starting treatment).

Pre-post treatment comparisons active depression

The number of patients with (i.e. HADS-D ≥ 8 and/or CES-D ≥ 16) and without active depression was calculated and a McNemar test was used to determine whether there was a difference in the proportion of patients with active depression at baseline and follow-up (T0 vs T1).

Relation migraine reduction and reduction in depressive symptoms

To investigate whether the benefit of treatment with anti-CGRP medication on depressive symptoms is due to anti-CGRP treatment or a reduction in mean monthly migraine days (MMD), two multiple linear regression models were used, one with HADS-D reduction as dependent variable and one with CES-D reduction, both with treatment and MMD reduction as independent variables. For treatment, we divided patients into anti-CGRP treatment (erenumab or fremanezumab) or control.

Response predictors

For erenumab and fremanezumab separately, two-way contingency tables were made for 'active depression' at baseline and the outcome of <50% or ≥50% reduction in monthly migraine days (MMD) in response to treatment. Chi-square test was used to determine whether there was an association between 'active depression' at baseline (T0) and the response to treatment. Furthermore, as an additional exploratory analysis this two-way contingency table was used to calculate the sensitivity, specificity, positive predictive value and negative predictive value of 'active depression' at baseline (T0) for prediction of a clinical response <50%.

Linear regression models were used to test associations, with age, gender, migraine days at baseline and the baseline responses of the above described questionnaires ('active depression', HIT-6, PSS, HSLC) as predictors and the absolute migraine reduction as a dependent variable. Analyses were run as multiple regression models, adjusting for the potential confounding effects of all variables that were tested.

For all analyses, two-tailed p-values ≤ 0.05 were considered as statistically significant. All analyses have been 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 patients provided written informed consent.

Data availability

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

Results

Literature search

In total 8 individual articles and abstracts were identified. The results of the literature search are presented in table e-1.

Baseline characteristics

The study population consisted of 110 patients that started treatment with erenumab, 117 patients that started treatment with fremanezumab, and 68 patients in the control group. All of these patients were invited to complete the questionnaires. Two patients discontinued erenumab after two months because of adverse events (severe daily nausea and general malaise). Of the remaining 108 erenumab patients, 101 responded to the questionnaires after three months (T1). In the study population of fremanezumab, no patients discontinued treatment before the 3 month period ended. In total 27 patients previously used erenumab and thus were excluded from the analyses. In total 78 patients responded to the questionnaires after three months (T1). The control group consisted of 68 patients. In all groups, on average patients had failed on five migraine preventives. Baseline characteristics for the different subgroups are presented in table 1. With the exception of patients fulfilling criteria for CM (at least 8 MMD with at least 15 MHD) there were no differences in demographics between the groups. A flowchart is presented in figure e-1.

Table 1 Patient baseline characteristics.

	Erenumab N = 108	**Fremanezumab N = 90**	**Control N = 68**
Female, n (%)	92 (85)	73 (81)	53 (78)
Age (years), mean ± SD	42.4 ± 12.5	44.5 ± 13.5	45.5 ± 9.9
MMD baseline, mean ± SD	14.0 ± 5.6	14.2 ± 6.3	14 ± 5.4
MHD baseline, mean ± SD	17.0 ± 6.2	17.2 ± 7.0	19.4 ± 5.7
MAMD baseline, mean ± SD	6.0 ± 3.6	5.4 ± 2.8	13.8 ± 5.9
HADS-D baseline, mean ± SD	7.7 ± 4.5	7.9 ± 4.6	7.9 ± 4.3
CESD baseline, mean ± SD	19.9 ± 11.1	19.2 ± 10.5	18.6 ± 11.7
Active depression, n (%)	75 (70)	55 (61)	45 (66)

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

Pre-post treatment comparisons depression

First, we looked at the number of patients with an active depression at baseline (T0) and at three months (T1). For erenumab, 70/101 (70%) patients were marked as having an active depression at T0, and 47/101 (47%) patients at T1. In the fremanezumab group, 46/78 (59%) patients fulfilled the criteria for active depression at T0, and 25/78 (32%) patients at T1. In the control group, 45/68 (66%) patients were marked as having an active depression at T0, and 43/68 (63%) patients at T1. Exact McNemar tests showed a reduction in the proportion of patients with active depression pre- and post-treatment (both $p<0.001$) for erenumab and fremanezumab, but not for control ($p=0.84$).

To visualize the change in HADS-D and CES-D, separated for erenumab and fremanezumab, we present our raw data in Figure 1 and 2.

Relation migraine reduction and reduction in depressive symptoms

We analyzed whether the reduction in HADS-D was dependent on anti-CGRP treatment while correcting for reduction in MMD. Reduction in HADS-D was positively associated with MMD reduction ($\beta = 0.16$, $p < 0.001$), but treatment with anti-CGRP medication had an additional effect on the reduction in HADS-D ($\beta = 2.45$, $p < 0.001$) (figure 3, table e-2) compared to control.

These analyses were repeated for CES-D, which showed similar results.

Predictive value of active depressive symptoms for <50% response

For erenumab, the proportion of patients with active depression differed between responder groups for erenumab (<50% versus ≥50% response) (Chi square test $p=0.02$, Table 2). Of the 75 patients who had signs of active depression (i.e. HADS-D ≥ 8 and/or CES-D ≥ 16) at baseline (T0), 58 (77%) patients had <50% reduction in monthly migraine days after three months of treatment with erenumab. Of the patients without active depression 18/33 (55%) had <50% reduction in monthly migraine days after three months of treatment with erenumab. Active depression had a sensitivity of 74%, a specificity of 46%, a positive predictive value of 77% and a negative predictive value of 45% for a clinical response to erenumab of <50%.

For fremanezumab, the proportion of patients with active depression did not differ between responder groups (<50% or ≥50% response) (Chi square test p = 0.09, Table 2).Of the 55 patients who had active depression before starting treatment with fremanezumab (T0), 27 (49%) patients had <50% reduction in migraine days after three months of treatment. Of the patients without active depression 22/35 (62%) had <50% reduction in monthly migraine days after three months of treatment with fremanezumab. Active depression had a sensitivity of 58%, a specificity of 27%, a positive predictive value of 63% and a negative predictive value of 19% for a clinical response to fremanezumab <50%.

Table 2 Active depression at baseline (T0) and response to erenumab and fremanezumab after three months of treatment.

Erenumab	**< 50% responders**	**≥ 50% responders**	
Active depression	58	17	75
No active depression	18	15	33
	76	32	108
Fremanezumab	**< 50% responders**	**≥ 50% responders**	
Active depression	27	28	55
No active depression	22	13	35
	49	41	90

Active depression = HADS-D ≥ 8 and/or CES-D ≥ 16. Erenumab: N = 108 (all patients who filled out questionnaires at baseline and completed the 3 months follow-up period. Chi square test p = 0.02. Sensitivity = 74%, specificity = 46%, positive predictive value (PPV) = 77%, negative predictive value (NPV) = 45% for a <50% response. Fremanezumab: N = 90 (all patients who filled out questionnaires at baseline and completed the 3 months follow-up period). Chi square test p = 0.28. Sensitivity = 55%, specificity = 32%, positive predictive value (PPV) = 49%, negative predictive value (NPV) = 37% for a <50% response.

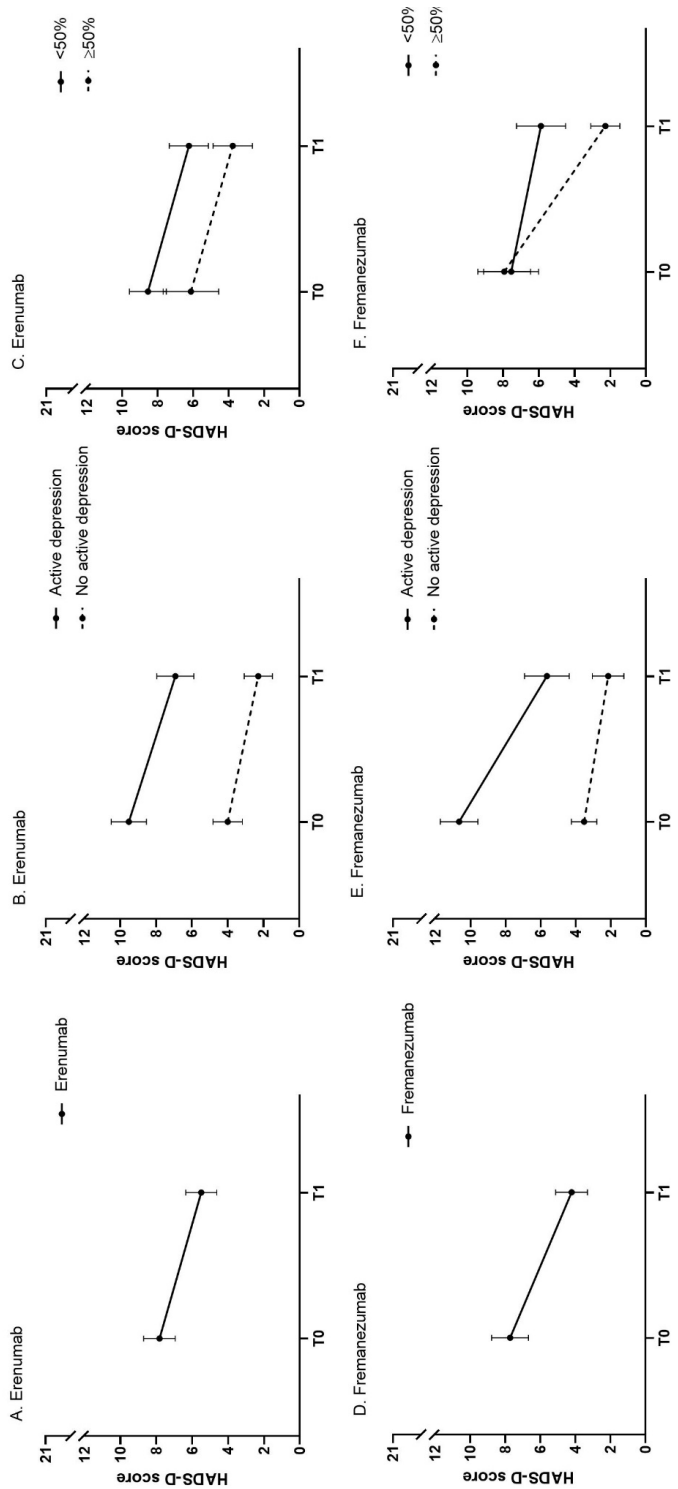

Figure 1 Mean HADS-D-score before (T0) and after (T1) treatment with erenumab (**A-C**) and treatment with fremanezumab (**D-F**). **A.** All patients treated with erenumab. **B.** Patients treated with erenumab with and without active depression at baseline (T0). **C.** Patients with ≥50% or <50% response to erenumab after three months. **D.** All patients treated with fremanezumab. **E.** Patients treated with fremanezumab with and without active depression at baseline (T0). **F.** Patients with ≥50% or <50% response to fremanezumab after three months. HADS-D score range 0-21. Active depression = HADS-D ≥ 8 and/or CES-D ≥ 16. Data presented in mean ± *95% CI*.

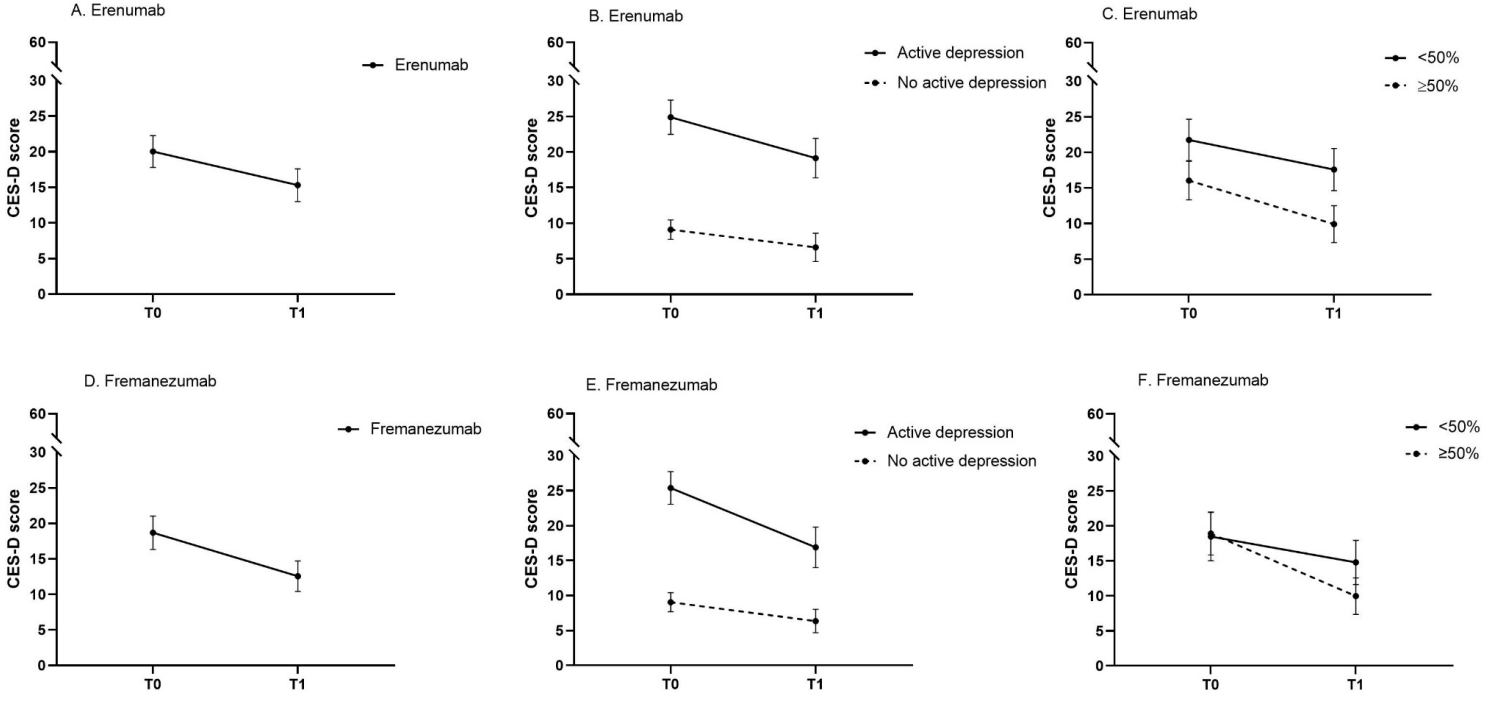

Figure 2 Mean CES-D score before (T0) and after (T1) treatment with erenumab (**A-C)** and treatment with fremanezumab (**D-F**). **A.** All patients treated with erenumab. **B.** Patients treated with erenumab with and without active depression at baseline (T0). **C.** Patients with ≥50% or <50% response to erenumab after three months. **D.** All patients treated with fremanezumab. **E.** Patients treated with fremanezumab with and without active depression at baseline (T0). **F.** Patients with ≥50% or <50% response to fremanezumab after three months. CES-D score range 0-60. Active depression = HADS-D ≥ 8 and/or CES-D ≥ 16. Data presented in *mean ± 95% CI.*

Response predictors

Table e-3 (left column) presents the results of the multiple linear regression analysis with absolute monthly migraine reduction (baseline vs month 3) as a response to erenumab as outcome variable. Migraine reduction in response to treatment with erenumab was negatively associated with active depression (β(CI)= -2.02 (-4.04 – -0.001), p=0.05), a higher HIT-6 score (β(CI) = -0.29 (-0.54 - -0.04), p=0.02) and a lower number of migraine days at baseline (β(CI)= 0.21 (0.06 – 0.36), p=0.01). Migraine reduction in response to treatment with fremanezumab was negatively associated with a lower number of migraine days at baseline (β(CI)= 0.31 (0.14 - 0.49), p<0.001, table e-3 right column).

Discussion

In this study we demonstrated a reduction in depressive symptoms in participants with migraine after three months of treatment with anti-CGRP medication. Importantly, this reduction in depressive symptoms was independent of the reduction in monthly migraine days. We found a negative association between active depression before starting treatment with erenumab and the clinical response.

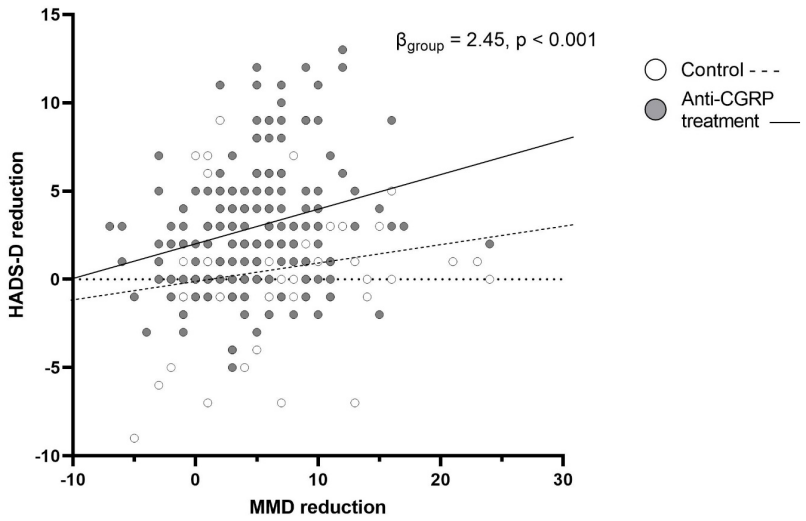

Figure 3 Relation migraine reduction and reduction in depressive symptoms. Reduction in HADS-D is positively associated with MMD (monthly migraine days) reduction, but treatment with anti-CGRP medication had an additional effect on the reduction in HADS-D (β = 2.45, p < 0.001) compared to control.

Decrease in depressive symptoms after start of preventive treatment has been described scarcely.[20-22] Although it might be presumed that depressive symptoms may improve when patients have less migraine attacks, our study suggests that anti-CGRP treatment has an additional effect on reducing depressive symptoms. Interestingly, migraine and (major) depressive disorder have shared genetic factors[1,3,23] and both have been associated with higher levels of CGRP.[1,23-26] CGRP-blocking medication might influence both migraine and depressive symptoms independently. However, the knowledge on effect of blockage of CGRP for depressive symptomatology is limited. While the anti-CGRP (receptor) antibodies most likely act peripherally, mood disorders have been associated with changes in several brain areas.[27] If erenumab and fremanezumab modify depressive symptoms independent from decrease in migraine days, this might suggest that central effects may be modified by a peripheral site of action. CGRP interacts with both the dopaminergic and noradrenergic systems in our brain, exerting several biochemical and behavioral effects.[28] Our study therefore demonstrates promising results for a new potential drug target for depression, however data is still limited.

There are only limited publications on the response to anti-CGRP treatment in subjects with a history of depression. In a brief communication on subjects with migraine treated with erenumab, researchers reported that psychological traits, such as depression, were not related to clinical outcome.[29] However, only a small sample size was investigated and treatment response was divided into three groups (non-responders, responders and super-responders), instead of a continuous outcome, leading to a great loss of power. Post-hoc analyses of phase 3 studies demonstrated that fremanezumab effectively reduced migraine frequency in subjects with comorbid depression as measured with the PHQ-9 questionnaire.[20,30] Even though these are interesting and important findings, they did not directly evaluate the effect of anti-CGRP medication on depressive symptoms, nor how depression influences responder rate. A post-hoc analyses of phase 3 studies of galcanezumab showed efficacy for reducing migraine frequency regardless of medical history of comorbid anxiety and/or depression.[31] The difference with our present study is that all anxiety and depression diagnoses, either ongoing or in the past, were included in those analyses and no separate data were presented as to what extent patients currently were affected by those disorders.

Interestingly, in literature there is evidence that cognitive behavior therapy for depression in people with migraine increases the response to preventive treatment.[32] Whether additional treatment of depression will lead to a more successful reduction in migraine in patients treated with CGRP-blocking medication is yet to be determined. The patient population in the present study had a high number of monthly migraine days and was resistant to previous preventive treatment. With this, the comorbidity of depressive symptoms was high, as to be expected. As the treatment options for this patient group are very limited, it is of utmost importance to increase the understanding of what it is that makes these patients (non-)responders and how to improve their migraine status and quality of life, including depressive symptoms.

A clear strength of the present study is the daily e-diary with automated algorithm. This gives an accurate assessment of the response to treatment. Even more because the time-locked aspect of the e-diary prevents patients from changing their answers or delaying their input, which prevents reporting bias. We evaluated the presence of depressive symptoms with the HADS-D and CES-D. Even though these questionnaires are not diagnostic tools for a clinical depression per se, they are indicative of depressive symptoms, and they provide for an easy screening tool for comorbid depression suitable for use in a headache clinic. A limitation of our study may be the sample size. In the fremanezumab group, patients already treated with erenumab were excluded. However, including these patients in the analyses (data not shown) did not influence the results. Furthermore, large commercial trials as opposed to investigator initiated studies might have more non-adherence, more heterogeneity in patient selection, more placebo-responders (particularly among late-enrolling patients), and inflation of the baseline scores, and therefore might have less sensitivity.[33,34] Another limitation might be that the control group was part of other concurring preventive studies which could potentially lead to selection bias. However, these patients were matched on active depression at baseline and had similar distribution in gender, age and migraine diagnosis and frequency, and failures on early preventative medication. We therefore believe that the control group was comparable to the erenumab and fremanezumab groups.

Conclusion

Depressive symptoms in subjects with migraine improve in response to anti-CGRP (receptor) monoclonals.

Clinical implications:

- In this study we demonstrated a reduction in depressive symptoms in participants with migraine after three months of treatment with anti-CGRP medication.
- Importantly, this reduction in depressive symptoms was independent of the reduction in monthly migraine days.
- We found a negative association between active depression before starting treatment with erenumab and the clinical response.
- Our study therefore demonstrates promising results for a new potential drug target for depression.

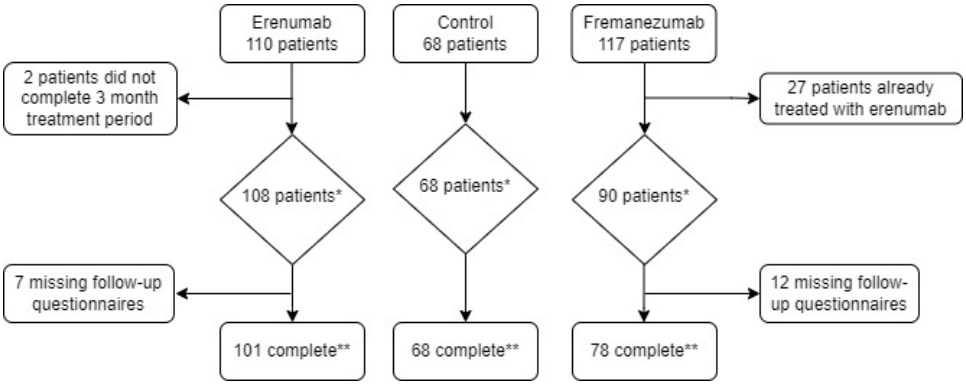

Figure e-1 Flowchart. *number of patients for linear regression analysis with migraine reduction as outcome. **number of patients used in pre-post treatment comparisons, and linear regression with HIT-6 reduction as outcome.

Table e-1 Results literature search on depression and monoclonal antibodies as treatment for migraine.

	Author	Title	Article type
Erenumab	Eghtesadi et al	Erenumab response in highly refractory migraine patients followed at a Canadian tertiary headache clinic: Preliminary results of a small case series at six months	Conference Abstract
	Tepper et al	Efficacy of erenumab for the treatment of patients with episodic migraine with depression and/or anxiety	Conference Abstract
	Russo et al	Multidimensional assessment of the effects of erenumab in chronic migraine patients with previous unsuccessful preventive treatments: A comprehensive real-world experience	Full article
Fremanezumab	Spierings et al	Improvements in quality of life and work productivity with up to 6 months of fremanezumab treatment in patients with episodic and chronic migraine and documented inadequate response to 2 to 4 classes of migraine-preventive medications in the phase 3b FOCUS study	Full article
	Lipton et al	Effects of fremanezumab in patients with chronic migraine and comorbid depression: Subgroup analysis of the randomized HALO CM study	Full article
	Driessen et al	Real-world effectiveness after initiating fremanezumab treatment in US patients with episodic and chronic migraine or difficult-to-treat migraine	Full article
Galcanezumab	Maizels et al	Assessment of anxiety and depression in a randomized, double-blind, placebo-controlled study of galcanezumab in adults with treatment-resistant migraine: Results from the conquer study	Conference Abstract
	Smitherman et al	Efficacy of Galcanezumab for Migraine Prevention in Patients With a Medical History of Anxiety and/or Depression: A Post Hoc Analysis of the Phase 3, Randomized, Double-Blind, Placebo-Controlled REGAIN, and Pooled EVOLVE-1 and EVOLVE-2 Studies	Full article

No relevant articles were found for eptinezumab. N = number of patients in analysis.
EM = episodic migraine, CM = chronic migraine. MOH = medication overuse headache.
PHQ-9 = Patient Health questionnaire. OLE = open-label extension. HADS = Hospital Anxiety and Depression Scale HADS-A = HADS – anxiety, HADS-D = HADS-depression.

Patients	Depression	Conclusion
N = 18 (EM = 13, CM = 5)	Definition = HADS-A AND or HADS-D ≥ 8. Assessment: At baseline and 6 months	1. 11% increase in number of patients with clinically positive anxiety and/or depression HADS-score 2. more patients with positive HADS at baseline in non-responder group (<50%)
N = 193 (all EM)	Definition: Self-reported history of depression and/or anxiety	Erenumab is efficacious in migraine patients with depression/anxiety
N = 70 (all CM)	Measured with: BDI-II, HDRS and HARS Assessed: at baseline, 3 months and 6 months	Significant improvement in depression and anxiety after 6 months treatment with erenumab
N = 807 (EM and CM)	Definition: PHQ-9 Assessed: at start and end of a 12-week open label extension	Improvement in depression symptomology (PHQ-9) during treatment with fremanezumab
N = 219 (all CM)	Definition: PHQ-9 score ≥ 10 at baseline Assessed: at baseline and week 12	1. Higher migraine day and headache day reduction with fremanezumab than placebo in patients with moderate to severe depression 2. Reduction in PHQ-9 after treatment with fremanezumab, but not significant compared with placebo
N EM = 416 N CM = 587	Definition: physician reported Major Depressive Disorder Assessed: at baseline	Fremanezumab is efficacious in migraine patients with major depressive disorder
N = 462 (EM and CM)	Determined with: PHQ-9 Assessed: at baseline and month 3	Decrease in PHQ-9 was greater in galcanezumab treated patients compared to placebo
N EM = 453 N CM = 311	Definition = current or past depression and/or anxiety based on available medical records and patient reporting.	1. in episodic migraine both galcanezumab doses lead to improvement in migraine days in patients with anxiety and/or depression. 2. in chronic migraine only the 240 mg dose lead to improvement in migraine days

Table e-2 multiple regression analysis with reduction in HADS-D or CES-D as outcome.

	Reduction in HADS-D		**Reduction in CES-D**	
Variable	**β-coefficient (95% CI)**	**p**	**β-coefficient (95% CI)**	**p**
Absolute reduction in MMD	0.16 (0.08 – 0.24)	**<0.001**	0.37 (0.15 – 0.59)	**0.001**
Treatment	2.449 (1.47 – 3.43)	**<0.001**	4.30 (1.74 – 6.86)	**0.001**

CI = confidence interval. Outcome = reduction in HADS-D and CES-D after three months (T1) compared to baseline (T0). Treatment = control (0) vs anti-CGRP (receptor) antibodies (1).

Table e-3 multiple regression analysis with migraine reduction as outcome.

	Erenumab (n = 108)		**Fremanezumab (n = 90)**	
Variable	**β-coefficient (95% CI)**	**p**	**β-coefficient (95% CI)**	**P**
Active depression	-2.02 (-4.04 – -0.001)	**0.05**	2.04 (-0.63 - 4.70)	0.13
Age	0.07 (0.003 – 0.14)	**0.04**	0.01 (-0.09 - 0.07)	0.73
Gender	2.20 (-0.08– 4.49)	0.06	2.16 (-0.43 - 4.76)	0.10
Migraine days baseline	0.21 (0.06 – 0.36)	**0.01**	0.31 (0.14 - 0.49)	**<0.001**
HIT-6	-0.29 (-0.54 - -0.04)	**0.02**	-0.10 (-0.45 - 0.26)	0.58
PSS	-0.04 (-0.19 – 0.12)	0.66	-0.15 (-0.35 - 0.04)	0.12
HSLC - Health care professional	0.06 (-0.06 – 0.18)	0.31	0.05 (-0.21 - 0.11)	0.55
HSLC – Internal	-0.06 (-0.15 – 0.02)	0.14	0.09 (-0.02 - 0.20)	0.11
HSLC – Chance	0.01 (-0.11 – 0.12)	0.90	-0.05 (-0.13 - 0.24)	0.58

CI = confidence interval. Outcome = absolute reduction migraine days month 3 after starting treatment with erenumab (left column) and fremanezumab (right column) compared to baseline. Active depression = HADS-D >= 8 and/or CES-D >=16. HIT = Headache Impact test. PSS = Perceived Stress Scale. HSLC = headache specific locus of control. All questionnaires answered at baseline.

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