Early Improvement of Affective, Fatigue and Allodynic Symptoms in a Cohort of Resistant Migraineurs Treated with Anti-CGRP/R Antibodies

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Article

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Abstract: Objective: The study aimed to evaluate the effects of monoclonal antibodies (mAbs) acting on the calcitonin gene-related peptide (CGRP) or its receptor (anti-CGRP/R mAbs) on comorbid symptoms of depression, anxiety, and fatigue in migraine patients resistant to traditional prophylaxis. **Methods:** The study was an open-label prospective study assessing comorbidities in patients with high frequency (HFEM) and chronic migraine (CM), medication overuse headache (MOH), and resistance to traditional prophylaxis treated with anti-CGRP/R mAbs for 3 months. **Results:** 77 patients were enrolled with either HFEM (21%) or CM (79%) with or without MOH (56% and 44% respectively). We identified 21 non-responders (27%) and 56 responders (73%), defined on the reduction ≥ 50% of headache frequency. The two groups were highly homogeneous for investigated comorbidities. Disease severity in terms of headache frequency, migraine-related disability, and affective comorbid symptoms were reduced in both groups with different thresholds; allodynia and fatigue were ameliorated only in responders. **Conclusion:** anti-CGRP/R antibodies improve pain together with affection, fatigue, and sensory sensitization in migraine patients.

Keywords: migraine; depression; anxiety; fatigue; comorbidities; monoclonal antibodies anti-CGRP/R

1. Introduction

Migraine ranks as the most prevalent, disabling, and long-term neurological disease [1]. Migraine is an evolutive disease, in which the clinical features can vary over a long time course, probably according to different pathophysiological mechanisms.

The prevalence of migraine in the general population is around 15%, and 8% of migraineurs suffer from chronic migraine (CM) [2,3]. CM is more burdensome than episodic migraine (EM) in terms of disability, quality of life, use of health resources, involvement of comorbidities, and drug resistance [4].

The comorbidity between migraine and psychiatric disorders was extensively explored in the literature. The strongest association was described with depression and anxiety, which seem to have a bidirectional relationship with migraine. Subjects with a combination of major depression and anxiety disorders are more likely to have migraine compared with those with depression or anxiety only and without both [5,6].

Fatigue has also been recognized as a dominant feature of migraine [7]. It is estimated that approximately 60% of migraineurs report pathologic fatigue. Furthermore, fatigue seems to be correlated with symptoms of depression and headache intensity in migraineurs [8].

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Depression, anxiety, and fatigue are pivotal elements of migraine-related disability and disease progression, regarded as risk factors for transforming EM into CM [9,10].

The prophylactic treatments for migraine can be also effective on psychiatric comorbidities (e.g. antidepressants) that are considered when choosing the proper drug for headache frequency control. The role of novel targeted anti-migraine drugs in this fearful triad (depression, anxiety, and fatigue) is still unclear and unpredictable based on the putative pathophysiological mechanism.

In this context, we evaluated comorbid symptoms of anxiety, depression, and fatigue at baseline and 3 months after starting a treatment with monoclonal antibodies (mAbs) acting on the calcitonin gene-related peptide (CGRP) (Fremanezumab, and Galcanezumab) or its receptor (CGRPR) (Erenumab) in a cohort of 77 subjects with a diagnosis of migraine resistant to traditional drug prophylaxis either high-frequency EM (HFEM > 8 headache days/month) or CM with or without medication-overuse headache (MOH). Additionally, we decided to consider anxiety-depressive symptoms and fatigue as potential prognostic factors for drug efficacy. Hence, we sorted the patients into two groups according to whether the treatment was clinically effective or not, to observe if any differences in these symptoms were present at baseline.

2. Methods

2.1. Study Design

The study was an open-label prospective study evaluating symptoms of anxiety, depression, and fatigue in 77 HFEM and CM patients resistant to traditional prophylaxis and therefore undergoing treatment with anti-CGRP/R mAbs (Erenumab 70 or 140 mg/month, Galcanezumab 120 mg/month, and Fremanezumab 225 mg/month, administered by subcutaneous injection once a month). The study consisted of a preliminary evaluation(V0) to verify the eligibility of the patient, a baseline assessment (V1) with the first administration of anti-CGRP/R mAbs, and a 3-month follow-up visit (V2).

2.2. Study Participants

We enrolled adult outpatients, consecutively enrolled from November 2021 to December 2022 in the Neurology Unit, Center for Diagnosis and Treatment of Headaches and Craniofacial Pain at the University of Pisa, suffering from HFEM or CM according to the International Classification of Headache Disorders – 3rd edition (ICHD-3) [11], and resistant to the common prophylaxis therapies according to the European Headache Federation (EHF) Consensus [12].

All patients received and failed at least three oral preventive medication classes (beta-blockers, calcium-channel blockers, anticonvulsants, antidepressants, onabotulinumtoxinA) due to a lack of efficacy or intolerable side effects.

Patients have discontinued other preventive treatments at least 3 months before the baseline or are treated with stable oral migraine prophylaxis (defined as stable dosage of the medication for at least 6 months before the inclusion visit and for the duration of the study). The exclusion criteria were: 1) age under 18; 2) diagnosis of schizophrenia, chronic psychosis, acute psychosis; 3) diagnosis of somatic and related symptom disorders; 4) diagnosis of ongoing substance use disorders; 5) patients with impaired speech; 6) patients with mental retardation; 7) diagnosis of other neurological diseases; 8) patients unable to provide valid written informed consent; 9) pregnant or breastfeeding patients; 10) patients with a desire to become pregnant during the study period.

This study was performed in accordance with the Declaration of Helsinki, and it was approved by the local ethics committee (Comitato Etico Area Vasta Nord Ovest—Sezione Autonoma del Comitato Etico Regionale per la Sperimentazione Clinica—Via Roma 67, 56126, Pisa, Italy) with approval code ID-14.518. All subjects involved provided written, informed consent before their inclusion.

2.3. Clinical Assessment

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The study visits were performed before (V1) and after (V2) the administration of the treatment. Clinical characteristics of migraine were collected through an interview and based on patients' self-reported diaries. Moreover, the following questionaries were administered at each visit: Migraine Disability Assessment (MIDAS) for the evaluation of migraine-related disability, Fatigue Severity Scale (FSS) to assess migraine-associated fatigue, the Generalized Anxiety disorder (GAD-7), and Patient Health Questionnaire (PHQ-9), to monitor anxiety and depressive symptoms, and Allodynia Symptoms Checklist 12 (ASC-12) to report ictal allodynia.

2.4. Statistical Analysis

All demographic and clinical data were presented for continuous variables in terms of medians and interquartile ranges.

The quantitative variables of the sample, evaluated with the Shapiro-Wilk test, do not have a normal distribution. For this reason, to test the possible differences before and after the treatment with anti-CGRP/R mAbs the Wilcoxon rank test was used, whereas to compare the two subgroups identified (responders and not-responders to anti-CGRP/R mAbs) the Mann-Whitney test was used.

Categorical variables were expressed as percentages and the comparison was performed by the chi-square test with continuity correction (Yates test). Binary logistic regression analysis was performed to predict the likelihood of the patients responding to the anti-CGRP/R mAbs, according to the measured variables.

The differences are considered statistically significant for values of probability $p < 0.05$ (two tails). SPSS version 24.0 for Windows was used for statistical analyses.

3. Results

The study population was composed of 77 patients, of which 59 (77%) were females, with a median age of 49,0 years old (IQR 15.0).

All patients were diagnosed with migraine without aura, 4 subjects (5%) had a concomitant diagnosis of migraine with aura. At baseline 16 patients (21%) self-reported a frequency compatible with HFEM, and 61 (79%) with CM of which 43 were also diagnosed with medication overuse headache (MOH). All patients were resistant to traditional drug prophylaxis.

All patients were treated with mAbs therapy: 44 patients (57%) received monoclonal antibodies acting on the CGRP (12 were treated with Fremanezumab and 32 with Galganezumab) and 33 patients (43%) received monoclonal antibodies acting on the CGRPR.

For all patients, we evaluated comorbidity symptoms of anxiety, depression, fatigue, and allodynia at baseline and 3 months after starting the treatment. All patients completed the study. No adverse events, tolerability, or safety issues were reported.

The overall analysis showed that the treatments were highly effective in reducing migraine frequency which dropped from a median of 23 days/month to 6 days/month ($p < 0.001$). The same highly significant impact was registered for migraine-related disability, anxiety and depressive symptoms, allodynia, and fatigue, as summarized in Table 1.

We decided to run a subgroup analysis dividing the population at baseline into two sets (responders and non-responders), based on the clinical effectiveness of the drugs measured at V2. According to the EHF treatment guidelines, non-responders were defined as subjects that did not have a reduction of at least 50% in the frequency of migraine after the administration of drugs for at least three months. We identified 21 non-responders (27%) and 56 responders (73%).

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Table 1. Clinical assessment at baseline and after 3 months.

	V1 Raw data		Clinical score (75-25 percentile)	V2 Raw data		Clinical score (75-25 percentile)	
	Median	75- 25 percentiles		Median	75- 25 percentiles		p[1]
Age (years)	47.00	57.00-41.00					
Headaches frequency (days/month)	23.00	30.00-15.00		6.00	13.00-4.00		**0.000***
MIDAS	93.00	133.00-69.00		24.50	49.00-4.00		**0.000***
ASC-12	6.00	10.25-3.75	Moderate (3.00-1.00)	3.00	6.75-.00	Mild (2.00-0.00)	**0.000 *#§**
GAD7	9.00	13.00-6.00	Mild (2.00-1.00)	6.50	8.50-3.75	Mild (1.75-0.00)	**0.000 *#§**
PHQ9	8.00	13.00-5.50	Mild (2.00-1.00)	6.00	9.00-3.00	Mild (1.00-0.00)	**0.000 *#§**
FSS	46.00	57.00-34.00		36.00	43.75-19.50		**0.000***

1 Test Wilcoxon; MIDAS: Migraine Disability Assessment Scale; FSS: Fatigue Severity Scale; ASC-12: Allodynia Symptom Checklist 12; GAD7: Generalized Anxiety Disorder 7; PHQ9: Patient Health Questionnaire 9; Clinical score:. Severe = 3; Moderate = 2; Mild = 1; Absent = 0; # raw data; § clinical score (* $p < 0.001$).

The two groups are homogeneous, without distinctive features among the analyzed variables. The burden of disease, the distribution of mild psychiatric symptoms (anxiety and depression), fatigue and ictal allodynia did not show significant differences (Table 2). The same result is obtained considering crude scores of the tests or clustering raw data according to validated clinical significance as absent, mild, moderate, and severe (from 0 to 3 in crescent order).

Table 2. Clinical features of responders and non-responders at baseline.

	Responder	Non-responder	
	N (%)		p[1]
EM	13 (17%)	3 (4%)	0.586
CM	43(56%)	18 (23%)	
with MOH	34 (44%)	9 (12%)	0.981
without MOH	22 (28%)	12 (16%)	
	Median (75- 25 percentiles)		p[2]
Age (years)	50.00 (57.00-43.50)	41.00 (49.00-36.00)	0.082
Headaches frequency (days/month)	22.00 (30.00-14.00)	30.00 (30.00-15.00)	0.237
MIDAS	90.00 (129.25-67.25)	99.00 (152.00-78.00)	0.171
ASC-12 (raw data)	6.00 (10.00-4.00)	5.00 (11.50-3.00)	0.812
ASC-12 (clinical score)	Moderate (3.00-1.00)	Mild (3.00-0.50)	0.628
GAD7 (raw data)	8.00 (12.50-6.00)	10.00 (14.00-6.00)	0.491
GAD7 (clinical score)	Mild (2.00-1.00)	Moderate (2.50-1.00)	0.250
PHQ9 (raw data)	7.50 (13.00-5.00)	10.00 (14.00-6.00)	0.132
PHQ9 (clinical score)	Mild (2.00-1.00)	Moderate-Mild (2.00-1.00)	0.259
FSS	45.00 (57.00-32.50)	54.00 (59.00-39.00)	0.151

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1 Chi-Squared test; 2 U Mann-Whitney test; MIDAS: Migraine Disability Assessment Scale; FSS: Fatigue Severity Scale; ASC-12: Allodynia Symptom Checklist 12; GAD7: Generalized Anxiety Disorder 7; PHQ9: Patient Health Questionnaire 9; EM: episodic migraine; CM: chronic migraine; MOH: medication overuse headache; Clinical score:. Severe = 3; Moderate = 2; Mild = 1; Moderate-Mild = 1.5; Absent = 0.

The responders' group exhibited a reduction of disease severity, non-exclusively in terms of headache frequency but also associated disability, allodynia ($p < 0.001$), and psychiatric comorbidities (Table 3).

Non-responders showed a significant reduction of the headache frequency although below the 50% threshold ($p=0.003$), and reduced migraine-related disability ($p < 0.001$). No significant improvement is registered for ictal allodynia, depressive symptoms, and fatigue. Although the raw scores for anxiety did not significantly change for this group, the clinical classification varied from a median value of *moderate* to *mild* symptoms during the 3 months of observation ($p = 0.034$).

However, the homogeneity of the groups did not allow for the prediction of treatment outcomes based on the investigated characteristics (Table 4).

Table 3. Differences between parameters at baseline and after three months in responders and non-responders.

	Responder Median (75- 25 percentiles)			**Non-responder Median (75- 25 percentiles)**		
	V1	**V2**	**p[1]**	**V1**	**V2**	**p[1]**
Headaches frequency (days/month)	22.00 (30.00-14.00)	5.00 (6.00-3.00)	**0.000*** **	30.00 (30.00-15.00)	20.00 (30.00-12.00)	**0.003****
MIDAS	96.00 (135.00-70.00)	8.00 (39.00-2.00)	**0.000*** **	99.00 (152.00-78.00)	38.00 (60.00-26.00)	**0.000*** **
ASC-12 (raw data)	6.00 (9.00-3.00)	1.50 (5.00-.00)	**0.000*** **	5.00 (12.00-2.00)	6.00 (9.00-1.00)	0.241
ASC-12 (clinical score)	Moderate (3.00-1.00)	Absent (1.00-.00)	**0.000*** **	Mild (3.00-.00)	Mild(3.00-.00)	0.476
GAD7 (raw data)	8.00 (12.00-6.00)	6.00 (7.00-3.00)	**0.001****	10.00 (13.00-5.00)	7.00 (10.00-6.00)	0.130
GAD7 (clinical score)	Mild (2.00-1.00)	Mild (1.00-.00)	**0.002****	Moderate (2.00-1.00)	Mild (2.00-1.00)	**0.034***
PHQ9 (raw data)	7.00 (12.25-5.00)	4.00 (7.00-2.00)	**0.000*** **	10.00 (14.00-6.00)	8.00 (13.00-6.00)	0.184
PHQ9 (clinical score)	Mild (2.00-1.00)	Absent (1.00-.00)	**0.000*** **	Mild-Moderate (2.25-1.00)	Mild (2.25-1.00)	0.414
FSS	43.50 (57.00-25.75)	29.00 (40.00-17.00)	**0.001****	54.00 (61.00-44.00)	42.00 (55.00-39.00)	0.109

1 Wilcoxon test; MIDAS: Migraine Disability Assessment Scale; FSS: Fatigue Severity Scale; ASC-12: Allodynia Symptom Checklist 12; GAD7: Generalized Anxiety Disorder 7; PHQ9: Patient Health Questionnaire 9; Clinical score:. Severe = 3; Moderate = 2; Mild = 1; Moderate-Mild = 1.5; Absent = 0 (*p<0.5; **p < 0.01; ***p < 0.001).

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Table 4. Logistic regression predicting the likelihood of responding to therapy with anti-CGRP/R mAbs at basaline (responders vs non-responders).

			95% CI	
	p	OR	Lower	Upper
Sex	0.223	0.406	0.095	1.731
Age	0.225	1.030	0.982	1.081
ASC 12	0.619	1.036	0.901	1.191
FSS	0.374	0,978	0.932	1.027
GAD 7	0.485	1.070	0.885	1.292
PHQ9	0.158	0.886	0.748	1.048

FSS: Fatigue Severity Scale; ASC-12: Allodynia Symptom Checklist 12; GAD7: Generalized Anxiety Disorder 7; PHQ9: Patient Health Questionnaire 9; OR: Odds Ratio.

4. Discussion

The overall analysis of the study charted that the efficacy of mAbs targeting the CGRP in a real-life study for migraine prevention is combined with a significant improvement in psychiatric symptoms. Noteworthy, the studied population is exclusively composed of HFEM or CM, resistant to the common drug prophylaxis prophylaxes (with or without the concomitant diagnosis of MOH).

A subgroup analysis was undertaken in patients who experienced ≥ 50% reductions in headache frequency (defined as responders) after anti-CGRP/R mAbs treatment to detect clinical predictive factors. The relationship between anxiety, depression, fatigue, and migraine, has been reported in several investigations. However, it is not clear whether the CGRP neurotransmission pathway may be directly involved in tuning affective symptoms [13]. The pain reduction due to anti-CGRP treatment could induce modification of "pain matrix" activity in the central nervous system and indirectly restore a neurotransmitter imbalance (e.g. serotonin and dopamine) pivotal for mood disorders [14]. CGRP could be related to chronic pain sensitization and cortical hyperexcitability, combined with other factors such as oxidation/reduction (redox) state [15–17]. In this framework, a chronic pain condition reporting several therapeutical failures represents *per se* a risk factor for psychiatric disease onset mining personal resilience.

Headache disorders, according to the global burden of disease (GBD) are the third most prevalent cause of global disability, expressed as years lived with disability (YLDs), just below depressive disorders if considering all genders and ages. The selection of young adults (age 15-49) of both genders makes headaches the most impacting condition in this stage of life, overcoming mood disorders [1].

Interestingly the responders and non-responders in this study had a similar age, burden of disease, and associated comorbidities. This evidence, on the one hand, further supports the homogeneity of the selected population and reduces the prognostic values of these characteristics but, on the other hand, suggest a common pathogenetic pathway between migraine and psychiatric comorbidities. This study provided additional evidence about mAbs anti-CGRP/R efficacy. In particular, the treatment consistently reduced allodynia, from moderate to absent in responders, whilst the non-responder group was unchanged. This observation may imply a modification of the central circuitry for the conscious perception of pain and cortical excitability [16,18,19], probably through the reduction of peripheral sensitization in responders [17,20,21]. Indeed, it was recently described that distinct thalamocortical circuits underlie allodynia induced by depression-like state rather than tissue damage [18].

Our study has some caveats. First, a precise psychiatric diagnosis was not extensively investigated. Then the sample number is relatively small though quite homogenous including only individuals reporting disabling migraine with a serious negative impact on daily life.

There was a remarkable reduction of MIDAS in responders (more than 10 folds from V1 values, see Table 3) with the median score classified as mild disability at V2. The non-responders also experienced a significant reduction of the MIDAS score (2.6 folds), being still over the threshold of severe disability (≥ 21). Both groups of patients had baseline scores of disabilities (median above 85),

substantially out-of-scale compared to the typical migraine patients. The cutoff levels are indeed difficult to apply, and the perceived amelioration of the personal disability was still of great impact also in non-responders.

The opposite can be said for anxiety and depressive symptoms. The responders' group showed, after three months of treatment, a significant reduction in the median values of the relative questionnaires, however, the scores of the symptoms can still be categorized as mild in GAD7 while passing from mild to absent for PHQ9 [22,23]. Notably, the anxiety symptoms for non-responders improved from moderate to mild during the period of the study ($p = 0.034$), even if crude scores showed a non-significant reduction ($p = 0.130$). This observation needs to be confirmed and considered with caution, as the responder and non-responder groups do not significantly differ for both clinical grading and scores of GAD7. Longer follow-up might detect if migraine modifications affect the onset or reduction of psychiatric symptoms or vice versa. However, the strict relationship between migraine, anxiety, and depressive disorders is confirmed in our study [24,25].

Fatigue that can be also subtended by thalamocortical dysfunctional mechanisms in migraine, notably was reduced only in the responders' group with a decrease of 33% from the baseline values [15,26–28]. The FSS scale has no clinically validated cutoffs. As for allodynia, it seems that the responders' group has a highly significant reduction, compared to non-responders. The FSS score reduction in migraine patients responding to anti-CGRP antibodies could be due to the improvement of the dysfunctional migraine-related mechanisms but could also suggest the potential role of CGRP neurotransmission in fatigue and dysfunctional pain-perception syndromes if these findings are replicated in further studies.

5. Conclusion

The role of the novel prophylactic agents for migraine targeting the CGRP system is not limited to the improvement of the disease severity but also affects anxiety, depressive symptoms, and fatigue. Among those conditions, allodynia and fatigue seem to be responsive to these treatments in those patients who experienced the highest clinical impact.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request.

Conflicts of Interest: The authors declare no conflict of interest.

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