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Predictors of Response to Anti-CGRP Monoclonal Antibodies: A Retrospective Study

Preditores de Resposta aos Anticorpos Monoclonais Anti-CGRP: Um Estudo Retrospetivo

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Abstract

Introduction: Anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies are effective and well-tolerated therapies for migraine prevention. However, up to 30%–40% of patients do not respond. While some clinical features have been associated with treatment outcomes, evidence remains limited.

Methods: We conducted a retrospective study of patients with episodic or chronic migraine followed at a tertiary headache center who initiated anti-CGRP therapy for the first time between April 2021 and April 2024. Patients received either erenumab 70 mg or fremanezumab 225 mg. Demographic and clinical data were collected. Treatment response was defined as a ≥50% reduction in monthly headache days at 3 months. Patients were classified as responders or non-responders. Group comparisons were performed using chi-squared tests for categorical variables and Student's t-test or Mann–Whitney test for continuous variables, according to data distribution.

Results: Sixty-eight patients were included (80.9% female; mean age 43.5 ± 11.5 years). Chronic migraine was present in 48.5%. Responders and non-responders did not differ significantly in age, sex, migraine type, baseline headache frequency, aura, unilateral pain, psychiatric comorbidities, medication overuse, prior preventive failures, or type of anti-CGRP antibody. Responders were more likely to report nausea and/or vomiting (76.6% *vs* 52.4%, p=0.008), whereas non-responders had a higher prevalence of vascular risk factors (33.3% *vs* 12.8%, p=0.046).

Conclusion: In our study, nausea/vomiting were associated with a favorable response to anti-CGRP therapy, replicating previous literature findings, while vascular risk factors were associated with non-response. These results suggest a potential interaction between vascular risk factors and CGRP-mediated mechanisms.

Resumo

Introdução: Os anticorpos monoclonais anti-calcitonin gene-related peptide (CGRP) são terapêuticas eficazes e bem toleradas na prevenção da enxaqueca. No entanto, cerca de 30%–40% dos doentes não respondem ao tratamento. Embora existam associações entre múltiplas variáveis clínicas e os resultados destas terapêuticas, a evidência disponível é limitada.

Métodos: Foi realizado um estudo retrospetivo com doentes com enxaqueca episódica ou crónica, seguidos num centro terciário, que iniciaram terapêutica anti-CGRP entre abril de 2021 e abril de 2024. Os doentes foram tratados com erenu-

mab 70 mg ou fremanezumab 225 mg. Foram recolhidas variáveis demográficas e clínicas. A resposta ao tratamento foi definida como uma redução ≥50% do número de dias de cefaleia por mês aos 3 meses e os doentes foram classificados como respondedores ou não respondedores. A análise estatística foi realizada utilizando o teste do qui-quadrado para variáveis categóricas e os testes t de *Student* e de Mann–Whitney para variáveis contínuas, de acordo com a distribuição dos dados.

Resultados: Foram incluídos 68 doentes (80,9% do sexo feminino; idade média 43,5 ± 11,5 anos). Cerca de 48,5% dos casos apresentavam enxaqueca crónica. Não se observaram diferenças significativas entre respondedores e não respondedores relativamente às variáveis idade, sexo, tipo de enxaqueca, frequência basal de cefaleias, presença de aura, dor unilateral, comorbilidades psiquiátricas, abuso medicamentoso, falência prévia de preventivos ou tipo de anticorpo anti-CGRP. Os respondedores apresentaram mais frequentemente náuseas e/ou vómitos (76,6% *vs* 52,4%; *p*=0,008), enquanto os não respondedores apresentaram uma maior prevalência de fatores de risco vascular (33,3% *vs* 12,8%; *p*=0,046).

Conclusão: Na nossa amostra, as náuseas/vómitos estiveram associadas a uma resposta favorável à terapêutica anti-CGRP, semelhante ao já descrito na literatura, enquanto os fatores de risco vascular associaram-se a uma não-resposta ao tratamento. Estes resultados sugerem uma potencial interação entre os fatores de risco vascular e os mecanismos mediados pelo CGRP.

Introduction

Anti-calcitonin gene-related peptide (CGRP) antibodies are effective and safe drugs for migraine treatment, as demonstrated by clinical trials and real-world studies.[1] However, given the high cost of these therapies and the fact that up to 30%-40% of patients do not respond, identifying predictors of treatment response is clinically valuable.[2] Previous studies have identified certain clinical features (e.g., episodic migraine, nausea/vomiting, response to triptans) as predictors of a favourable response, while others (e.g., chronic migraine, obesity, and psychiatric comorbidities) have been associated with lower efficacy.[2,3] Despite these findings, the literature on predictors of response to anti-CGRP antibodies remains limited, and further evidence is needed. This study aims to compare patients with migraine who responded to anti-CGRP antibodies with those who did not, to identify potential predictors of treatment response.

Methods

We conducted a retrospective study of patients with episodic or chronic migraine followed at a tertiary headache center who initiated anti-CGRP therapy (erenumab 70 mg or fremanezumab 225 mg) between April 2021 and April 2024; these two monoclonal antibodies were the only anti-CGRP available at our center during the study period, and their selection was based solely on availability. The inclusion criteria were age ≥ 18 years, a diagnosis of episodic or chronic migraine according to the International Classification of Headache Disorders-3 (ICHD-3) criteria, initiation of erenumab or fremanezumab as preventive treatment, and follow-up of at least 3 months. We excluded patients who did not complete 3 months of follow-up, those who discontinued anti-CGRP therapy before completing 3 months of treatment, and cases with missing data on the number of headache days. Demographic and clinical data were collected based solely on electronic clinical records at baseline (last appointment before treatment with anti-CGRP antibodies) and 3 months after the initiation of anti-CGRP antibodies. Headache days were measured using headache calendars provided to patients. Treatment response was defined as ≥50% reduction in monthly headache days at 3 months. Patients were categorized as responders or non-responders. Vascular risk factors were defined as the presence of one or more of the following: hypertension (≥140/90 mmHg), hyperlipidemia (total cholesterol ≥240 mg/dL or LDL ≥190 mg/dL), type 2 diabetes mellitus (fasting glucose ≥126 mg/dL or HbA1C ≥6.5%), tobacco use, or overweight

(BMI ≥25). Analgesic medication overuse was defined as intake of NSAIDs ≥15 days/month for >3 months or triptans ≥10 days/month for >3 months. Patients were considered NSAID or triptan responders if they were headache-free within 2 hours after intake in at least ≥50% of the migraine episodes. Categorical variables were compared using chi-squared tests, while continuous variables were compared using Mann–Whitney tests (for non-normally distributed data) or Student's t-test (for normally distributed data). Normality was assessed using the Shapiro-Wilk test. In cases of missing data, analyses were performed using available data for each variable. Overall, the proportion of missing data across included cases was <2%. SPSS Statistics version 29.0 was used for the statistical analysis.

Results

A total of 68 patients were included, 80.9% were female, with a mean age of 43.5+/-11.5 years old. Thirty-three patients (48.5%) had chronic migraine, and 20 patients (29.4%) had migraine with aura. The baseline median headache frequency (IQR) was 14 days/month (11.0). Patients started anti-CGRP treatment with either erenumab 70 mg (57.4%) or fremanezumab 225 mg (42.6%). Forty-one patients (60.3%) had unilateral pain, and 47 patients (69.1%) had associated nausea/vomiting. In our cohort, 16 patients (23.5%) had psychiatric comorbidities, 13 patients (19.1%) had vascular risk factors, and 36 (52.9%) had analgesic medication-overuse. Regarding prior treatments, 37 patients (54.4%) responded to NSAIDs or triptans. Preventive history showed a median of 4 prior oral preventive failures, with 13 patients (19.1%) having failed onabotulinumtoxinA. A full characterization of the study population is presented in **Table 1**. Responders and non-responders did not differ significantly in age, sex, migraine type, baseline headache frequency, aura, unilateral pain, psychiatric comorbidities, medication overuse, prior treatment failure, or type of anti-CGRP. However, responders were more likely to have nausea/

Table 1. Study population characterization.

	Total (n=68)	Responders (n=47)	Non-responders (n=21)	*p*-value
Age, mean (SD)	43.5 (11.5)	44.1 (12.1)	42.3 (10.3)	0.560
Age >50 years, n (%)	23 (33.8)	17 (36.2)	6 (28.6)	0.541
Age (headache onset), median (IQR)	15.0 (6.5)	15.0 (6.0)	14.0 (9.8)	0.865
Female, n (%)	55 (80.9)	36 (76.6)	19 (90.5)	0.160
Migraine type, n (%)				0.671
Chronic migraine	33 (48.5)	22 (46.8)	11 (52.4)	
Episodic migraine	35 (51.5)	25 (53.2)	10 (47.6)	
Baseline monthly headache days, median (IQR)	14.0 (11.0)	14.0 (11.0)	15.0 (11.0)	0.858
Aura, n (%)	20 (29.4)	13 (27.7)	7 (33.3)	0.757
Unilateral pain, n (%)	41 (60.3)	29 (61.7)	12 (57.1)	0.420
Nausea/vomiting, n (%)	**47 (69.1)**	**36 (76.6)**	**11 (52.4)**	**0.008**
Vascular risk factors, n (%)	**13 (19.1)**	**6 (12.8)**	**7 (33.3)**	**0.046**
Psychiatric comorbidities, n (%)	16 (23.5)	9 (19.1)	7 (33.3)	0.203
Medication-overuse, n (%)	36 (52.9)	24 (51.1)	12 (57.1)	0.772
Response to NSAIDs, n (%)	37 (54.4)	24 (51.1)	13 (61.9)	0.643
Response to triptans, n (%)	37 (54.4)	27 (57.4)	10 (47.6)	0.249
OnabotulinumtoxinA failure, n (%)	13 (19.1)	8 (17.0)	5 (23.9)	0.511
Prior preventive failures, median (IQR)	4.0 (1.0)	4.0 (2.0)	4.0 (1.0)	0.567
Concurrent number of preventives, median (IQR)	1.0 (2.0)	1.0 (1.5)	1.0 (2.0)	0.878
Anti-CGRP antibody, n (%)				0.981
Erenumab	39 (57.4)	27 (57.4)	12 (57.1)	
Fremanezumab	29 (42.6)	20 (42.6)	9 (42.9)	

Abbreviations: SD, standard deviation; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; CGRP, calcitonin gene-related peptide.

vomiting (76.6% *vs* 52.4%; *p*-value 0.008), while non-responders had a higher prevalence of vascular risk factors (33.3% *vs* 12.8%; *p*-value 0.046).

Discussion

Our findings replicated previous data showing that nausea/vomiting are associated with better anti-CGRP response (with erenumab and fremanezumab).[2,3] Notably, we identified that vascular risk factors are associated with non-response to anti-CGRP antibodies, an association not previously reported, except for isolated findings related to obesity in galcanezumab-treated patients.[2,3] The relation between anti-CGRP and vascular risk factors is complex and not yet fully understood. CGRP is a neuropeptide that plays a key role in vascular homeostasis, acting as a potent vasodilator and contributing to cardiovascular protection.[4,5] Anti-CGRP monoclonal antibodies act by targeting either the CGRP receptor (e.g. erenumab) or the CGRP ligand (e.g. fremanezumab), thereby blocking its vasodilatory effects, which may contribute, at least in part, to their therapeutic efficacy in migraine prevention.[4] In the presence of chronic vascular stress, such as hypertension, diabetes mellitus, hyperlipidemia, or obesity, vascular remodeling, endothelial dysfunction, and increased arterial stiffness may occur, leading to a reduction in vasodilatory reserve of cerebral arteries and arterioles.[5,6] In this context, experimental data suggest that CGRP expression and receptor activity may be upregulated as a compensatory response to vascular dysfunction.[7] Consequently, blocking the CGRP pathway in patients with vascular risk factors could result in a greater hemodynamic impact compared with patients without such risk factors, due to a reduced residual vasodilatory capacity in structurally remodeled vessels. This may contribute to reduced therapeutic efficacy in this subgroup, as the vascular substrate available for modulation is already compromised. Limitations of this study include a relatively small sample size, its retrospective design, the availability of only two anti-CGRP antibodies at our center, and the categorization of vascular risk factors as a broad variable that does not account for the severity of individual risk factors or the cumulative risk in patients with multiple risk factors. Consequently, our findings should be interpreted as statistical associations rather than definitive evidence of prediction, and they require confirmation in larger studies. ■

Contributorship Statement / Declaração de Contribuição

VMF: Research, statistical analysis, organization, and elaboration of the manuscript.

MS: Research, statistical analysis, and revision of the manuscript.

AC and MVB: Organization, conception, and revision of the manuscript.

GC: Research, conception and study design, organization, elaboration and revision of the manuscript.

All authors approve the final version to be published.

VMF: Pesquisa, análise estatística, organização e elaboração do manuscrito.

MS: Pesquisa, análise estatística e revisão do manuscrito.

AC e MVB: Organização, conceção e revisão do manuscrito.

GC: Pesquisa, conceção e desenho do estudo, organização, elaboração e revisão do manuscrito.

Todos os autores aprovam a versão final a ser publicada.

Responsabilidades Éticas

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

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References / Referências

1. Murray AM, Stern JI, Robertson CE, Chiang CC. Real-World Patient Experience of CGRP-Targeting Therapy for Migraine: a Narrative Review. Curr Pain Headache Rep. 2022;26:783-94. doi:10.1007/s11916-022-01077-z
2. Sánchez-Rodríguez C, Gago-Veiga AB, García-Azorín D, Guerrero-Peral ÁL, Gonzalez-Martinez A. Potential Predictors of Response to CGRP Monoclonal Antibodies in Chronic Migraine: Real-World Data. Curr Pain Headache Rep 2024;28:1265-72. doi: 10.1007/s11916-023-01183-6.
3. Schoenen J, Van Dycke A, Versijpt J, Paemeleire K. Ten open questions in migraine prophylaxis with monoclonal antibodies blocking the calcitonin-gene related peptide pathway: a narrative review. J Headache Pain. 2023 Aug 1;24(1):99. doi: 10.1186/s10194-023-01637-7.
4. Favoni V, Giani L, Al-Hassany L, Asioli GM, Butera C, de Boer I, et al. CGRP and migraine from a cardiovascular point of view: what do we expect from blocking CGRP? J Headache Pain. 2019;20:27. doi: 10.1186/s10194-019-0979-y.

5. Russell FA, King R, Smillie SJ, Kodji X, Brain SD. Calcitonin gene-related peptide: physiology and pathophysiology. Physiol Rev. 2014;94:1099-142. doi:10.1152/physrev.00034.2013.

6. Mouches P, Langner S, Domin M, Hill MD, Forkert ND. Influence of cardiovascular risk-factors on morphological changes of cerebral arteries in healthy adults across the life span. Sci Rep. 2021;11:12236. doi:10.1038/s41598-021-91669-3

7. Smillie SJ, Brain SD. Calcitonin gene-related peptide (CGRP) and its role in hypertension. Neuropeptides. 2011;45:93-104. doi:10.1016/j.npep.2010.12.002.