Check for updates

Received: 6 September 2025 | Accepted: 10 February 2026

DOI: 10.1111/head.70086

RESEARCH SUBMISSION

Evaluation of the effectiveness and safety of anti-CGRP monoclonal antibodies in patients with migraine and autoimmune diseases: IMMUNO-CGRP study

María Clara García-Castillo[1,2] | Álvaro Sierra-Mencía MSc[3,4] | Edoardo Caronna MD PhD[5,6] | Daniel Toledo-Alfocea MD[7] | Alex Jaimes MD[1,8] | Sarai Urtiaga MD[9] | Javier Casas-Limón MD[10] | Albert Muñoz-Vendrell MD PhD[11] | Sonia Santos-Lasaosa MD PhD[12] | Valvanuz García Martín MSc[13] | Guillermo Martín Ávila MD[14] | Marcos Polanco MD[15] | Maria Dolores Villar-Martínez MD[16] | Cristina Trevino-Peinado MD[17] | Laura Rubio-Flores MD[18] | Antonio Sánchez-Soblechero MD[19] | Leonardo Portocarrero Sánchez MD[20] | Elisa Luque-Buzo MD[19] | Alberto Lozano-Ros MD PhD[19] | Ana Beatriz Gago-Veiga MD PhD[1,21,22] | Javier Díaz-De-Terán MD PhD[1,20] | Andrea Recio García MSc[3,4] | Javiera Canales Rodríguez MD[5,23] | Andrea Gómez García MD[8] | Marta González Salaices MD[9] | Sergio Campoy MD[11,24] | Ane Mínguez-Olaondo MD PhD[25,26,27] | Stefania Maniataki BSc[16] | Vicente González-Quintanilla MD PhD[15] | Jesús Porta-Etessam MD PhD[8,28] | María-Luz Cuadrado MD PhD[29] | Ángel Luis Guerrero Peral MD PhD[3,4,30] | Patricia Pozo-Rosich MD PhD[5,6] | Jaime Rodríguez-Vico MD[8] | Mariano Huerta-Villanueva MD[11,24] | Julio Pascual MD PhD[15] | Peter J. Goadsby MD PhD[31] | Alicia Gonzalez-Martinez MD PhD[1,2,21]

Correspondence
Alicia Gonzalez-Martinez, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid, Calle Diego de León 62, Madrid, Spain.
Email: alicia.gonzalez.martinez@live.com

Funding information
Instituto de Salud Carlos III, Grant/Award Number: CM21/00178, JR23/00005 and

Abstract

Objective: This study aimed to evaluate demographic characteristics, treatment effectiveness, and safety outcomes in patients with migraine undergoing anti-calcitonin gene-related peptide (CGRP) treatments regarding the presence of autoimmune diseases.

Background: CGRP has an important role in migraine pathophysiology through neuronal modulation in the trigeminovascular nociceptive system and activation of neuroinflammatory cascades. We hypothesized that autoimmune diseases may influence

Abbreviations: AD, autoimmune diseases; CGRP, calcitonin gene-related peptide; CGRP mAbs, monoclonal antibodies against CGRP; MHD, monthly headache days; MMD, monthly migraine days; SD, standard deviation.

For affiliations refer to page 9.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2026 The Author(s). *Headache: The Journal of Head and Face Pain* published by Wiley Periodicals LLC on behalf of American Headache Society.

PI24/01085; European Union (FEDER/European Regional Development Fund-"A way to make Europe")

treatment response and safety profiles in patients with migraine treated with anti-CGRP treatments.

Methods: This was a retrospective multicenter, age- and sex-matched cohort study in headache units/headache clinics in Spain and United Kingdom between May 2024 and May 2025 including patients treated with CGRP monoclonal antibodies from prospectively collected cohorts. Patients were assessed for demographics, migraine-related characteristics, treatment effectiveness (monthly migraine days [MMD] and/or monthly headache days [MHD]), and safety outcomes. The main outcome was the effectiveness measured by ≥50% response rate in MMD between the two groups. Secondary outcomes included other effectiveness measurements regarding the number of MMD and MHD and treatment emerging adverse events.

Results: A total of 388 patients with migraine under anti-CGRP treatments (194 with autoimmune diseases and 194 age- and sex-matched controls without autoimmune diseases) were included. The proportion of patients achieving a ≥50% response rate in MMD was higher in patients without autoimmune diseases at 6 (69% vs. 53%; $p=0.006$) and 9 months (74% vs. 52%; $p=0.006$). Treatment emerging adverse events were comparable between the two groups (35% vs. 38%; $p=0.575$). Patients with autoimmune disease had a significantly lower likelihood of achieving a ≥50% response in MMD compared with those without autoimmune disease (adjusted odds ratio, 0.61; 95% confidence interval, 0.44–0.85; $p=0.006$), independent of comorbid depression and medication overuse.

Conclusions: Our study shows that anti-CGRP treatments are effective and safe for patients with migraine regardless the presence of autoimmune diseases, although an increased treatment response in patient without autoimmune disorders compared to patients with autoimmune disorders was observed. These findings highlight the need for early intervention, tailored strategies, and vigilant monitoring in patients with migraine and autoimmune disorders. Further research should explore immunomodulatory approaches to enhance outcomes.

Plain Language Summary

Recent studies have found an association between migraine and several chronic inflammatory diseases, such as multiple sclerosis, inflammatory bowel disease, and rheumatoid arthritis, suggesting that these conditions might share common immune and vascular pathways. This study compared the safety and effectiveness of anti-calcitonin gene-related peptide treatments in patients with migraine who also have autoimmune disease with those who do not have autoimmune disease. Patients with autoimmune diseases did not respond as well to the medications but had similar side effects, suggesting that close monitoring and personalized care are needed for patients with migraine who also have autoimmune disorders.

KEYWORDS
anti-CGRP, autoimmunity, immunomodulatory, migraine, neuroinflammation, safety

INTRODUCTION

Migraine is a complex neurological disease with a prevalence of 14%–15% that represents the second cause of disability worldwide.[1] Calcitonin gene-related peptide (CGRP) has an important role in migraine pathophysiology. It is involved in neuronal modulation in the trigeminovascular nociceptive system and activation of neuroinflammatory cascades.[2]

Regarding the immunomodulatory role of CGRP, recent studies have shown that CGRP signaling leads to a global inhibition of innate

15264610, 0, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.70086 by Universidad De Zaragoza, Wiley Online Library on [07/04/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

immunity and increasing serum CGRP levels in situations of systemic inflammation have been found.[3] This peptide is released from sensory C-fibers and acts on adjacent cells like monocytes/macrophages, mast cells, or Langerhans' cells, and it regulates cytokine production by modulating the differentiation of CD4 lymphocytes away from the Th1 and Th17 pathways, which are involved in diseases such as rheumatoid arthritis.[4] On vascular smooth muscle cells, CGRP induces vasodilation and has an anti-proliferative effect; whereas, on endothelial cells, it promotes proliferation and angiogenesis and attenuates leukocyte adhesion.[5,6] Moreover, CGRP also plays a role in host defense against a broad range of infective agents.[7] Several symptoms affecting multiple organs have been reported in patients both with and without a history of inflammatory disease.[3] CGRP is believed to negatively regulate innate immunity, limiting inflammatory damage, although it may promote immunosuppression in severe infections such as sepsis.[7,8] These effects highlight CGRP's potential as a regulator of the immune system beyond its neurological involvement in migraine, and may explain the inflammatory and infectious complications observed in patients treated with monoclonal antibodies against CGRP (CGRP mAbs).[3,7,8]

Recent studies have found an association between migraine and several chronic inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease (IBD), suggesting that inflammatory, immunological, and vascular mechanisms shared by these conditions could underlie this connection.[9–14] This bidirectional association emphasizes the potential importance of understanding the impact behind CGRP inhibition in patients with autoimmune diseases (AD) whose inflammatory state may call for higher doses of CGRP mAbs, and highlights the necessity of further research in this area. Moreover, a higher prevalence of migraine has been found in autoimmune disorders such as multiple sclerosis[12,15,16] and IBD,[10,17–19] suggesting a link between inflammatory disorders and migraine.

To date, there is scarce evidence regarding the real-world effect of the potential immunomodulatory role of CGRP that comes from a limited number of studies,[3,18–20] emphasizing the urgent need for further research that examines the repercussions of blocking CGRP in patients with AD and highlighting the importance of this present project for filling that knowledge gap.

We hypothesized that comorbid AD may impact treatment response and safety profiles in patients with migraine undergoing anti-CGRP therapy. Our principal objective is to evaluate the response and tolerability of the anti-CGRP drugs in patients with migraine and AD. As a secondary objective, we evaluated other effectiveness measurements, tolerability profile, and explored independent factors associated with patients with migraine and comorbid AD.

MATERIALS AND METHODS

Ethics statement

Approval for the study protocol including written informed consent was obtained from the institutional ethics committee of Hospital Universitario de la Princesa (no. 4563). This study represents the primary, a priori-planned analysis of these data and was designed as a sex- and age-matched cohort study before examination of study outcomes. All analyses were conducted in accordance with prespecified study objectives, and no prior publications have reported analyses addressing the research question examined in the present study.

Study design

This is a multicenter retrospective study that includes patients with migraine and AD treated with anti-CGRP drugs and age- and sex-matched control patients with migraine and no AD collected in prospective cohorts of patients with migraine attended at headache units/headache clinics in Spain and United Kingdom between May 2024 and May 2025 from CGRP monoclonal antibodies cohort databases at headache units and clinics, including only patients fulfilling inclusion criteria. Migraine diagnosis was made by neurologists with experience in treating headache disorders according to the International Classification of Headache Disorders, 3rd edition[21] and prescription of anti-CGRP drugs followed the European guidelines recommendations.[22]

The inclusion criteria for patients with AD treated with anti-CGRP drugs were: (1) 18 years of age or older; (2) a confirmed diagnosis of migraine; (3) ongoing treatment with anti-CGRP medications with available baseline data and at least one follow-up assessment at 3 or 6 months for either monthly migraine days (MMD) or monthly headache days (MHD); and (4) the presence of one or more autoimmune disorders. These included neurological diseases (multiple sclerosis, myasthenia gravis, and autoimmune encephalitis), rheumatological conditions (rheumatoid arthritis, Raynaud's phenomenon, systemic lupus erythematosus, Sjögren's syndrome, polymyalgia rheumatica, and vasculitis), gastrointestinal disorders (inflammatory bowel disease and autoimmune hepatitis), dermatological conditions (psoriasis and cutaneous lupus), endocrine disorders (hyperthyroidism, hypothyroidism, and diabetes mellitus type 1), and autoimmune-linked hypersensitivity syndromes (asthma, hereditary angioedema, and chronic urticaria) with specialists-confirmed diagnosis following appropriate criteria for each of the conditions. Exclusion criteria were (1) refusal to participate in the study, and (2) contraindications for the use of anti-CGRP drugs.

Study cohort

Patients were consecutively included from respective anti-CGRP databases, with selection criteria based on clinical records and eligibility for anti-CGRP therapies. Patients with AD were patients under anti-CGRP therapies (erenumab, fremanezumab, galcanezumab, or eptinezumab) with AD. Patients without AD were age- (±5 years) and sex-matched patients with anti-CGRP treatments with no AD.

15264610, 0, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.70086 by Universidad De Zaragoza, Wiley Online Library on [07/04/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Variables included in the study

Demographic and clinical variables included sex, age, the presence of high blood pressure, dyslipidemia, diabetes, smoking, current alcohol consumption, anxiety, depression, insomnia, other relevant comorbidities according to the diagnosis of the physician in charge, age of migraine onset, migraine type (episodic or chronic according to International Classification of Headache Disorders, 3rd edition criteria), presence of aura, duration of migraine, duration of chronic migraine, medication overuse, and the number of prior preventive treatments. The study also examined treatment response measured by the ≥50% response rate in MMD and MHD, the presence of adverse events, disease activity, and worsening of autoimmune conditions (measured by clinical worsening according to the physician in charge, analytical worsening or new MRI lesions). All data were managed in a pseudonymized manner.

Statistical analysis

Data distribution was first assessed using the Kolmogorov–Smirnov test to evaluate normality. Descriptive statistics were reported according to data type and distribution. Symmetrically distributed continuous variables are presented as means with standard deviations (SDs), skewed continuous variables as medians with interquartile ranges, and categorical variables as counts with percentages. Group comparisons were conducted using appropriate parametric or nonparametric statistical tests according to variable type, number of groups, and distributional assumptions. Comparisons of continuous variables were performed using Student's *t*-test or the Wilcoxon rank-sum test, and categorical variables using χ^2 or Fisher's exact tests. Where applicable, adjustments for multiple comparisons were performed using Bonferroni correction. To evaluate treatment response, we analyzed potential differences in the percentage of patients achieving ≥50% response rate in MMD and also ≥50% response rate in MHD, MMD, and MHD between patients with and without AD. For this, we performed generalized estimating equation (GEE) models using the logarithm of ≥50% response rate in MMD, ≥50% response rate in MHD, MMD, and MHD including depression, and medication overuse as confounding variables. In addition, we evaluated the group-by-time interaction. Moreover, an exploratory logistic regression model was developed to identify variables independently associated with patients under anti-CGRP therapies in the presence of AD. Initially, all variables of interest were included in the analysis. A stepwise approach was used to refine the model, systematically removing nonsignificant variables ($p > 0.05$) while retaining those with statistical and clinical relevance. To assess the goodness of fit, the Hosmer-Lemeshow test was applied. Linearity and multicollinearity were assessed by graphical inspection and variance inflation factors. The SPSS version 16.0 (IBM Corp., Armonk, NY, USA) for Windows and R version 4.3.1(R Foundation for Statistical Computing, Vienna, Austria) including compareGroups and *gtsummary* packages were used for statistical analysis. GraphPad Prism v. 9.5.1 (GraphPad Software Inc., La Jolla, CA, USA) was used for the figures. We used a convenience sample based on data available and did not conduct a sample size calculation. *p* values presented are for a two-tailed test, and we considered *p* values <0.05 as statistically significant. Missing data were not imputed. Complete case analysis was performed for the multivariable models.

RESULTS

Baseline characteristics

A total of 388 patients were included in the study. The mean age of the cohort was 49.3 years (SD, 10.2). The majority of the cohort was female (92.8%, 360 of 388). Key baseline characteristics and comorbidities are summarized in Table 1.

The most prevalent comorbid conditions included anxiety (39.2%, 152 of 388) and depression (35.8%, 139 of 388). Additionally, 14.4% (56 of 388) of the patients had hypertension, 15.2% (59 of 388) had dyslipidemia, and 2.3% (9 of 388) had diabetes mellitus. Lifestyle factors included active smoking in 19.1% (74 of 388) of the population.

The main AD were rheumatological (35%, 68 of 194), neurological (11%, 22 of 194), hyper/hypothyroidism (25%, 49 of 194), and gastrointestinal (19%, 37 of 194). Table 2 provides a detailed breakdown of autoimmune disorders. Among AD with more than 10 patients per category, the most frequent were hypothyroidism ($n = 39$), rheumatoid arthritis ($n = 28$), multiple sclerosis ($n = 18$), systemic lupus erythematosus ($n = 16$), Crohn's disease ($n = 16$), and ulcerative colitis ($n = 15$). Thirty-nine patients were considered to have active AD.

Migraine-specific characteristics showed that chronic migraine was diagnosed in 81.4% (316 of 388) of the patients, with 26.9% (104 of 388) reporting migraine aura. The mean time living with migraine was 28.3 years (SD, 13), whereas the mean time with chronic migraine was 10.9 months (SD, 9.9). Medication overuse was identified in 65.8% (254 of 388) of patients. Patients underwent an average of 5.4 preventive treatments before anti-CGRP therapies (SD, 2.5).

Overall, there was a mean number of MHD of 22 (SD, 7.5) and a mean number of MMD of 15 days (SD, 7) at baseline. A ≥50% response rate in MMD was achieved by 194 of 318 (61%) at 6 months. The overall adverse event rate was 139 of 384 (36.2%), the most common being constipation (72 of 139; 52%), injection site reaction (43 of 139; 31%), and dizziness (40 of 139; 29%).

Demographic and clinical characteristics in patients with and without autoimmune disorders

Patients with AD demonstrated similar demographic and clinical characteristics to the non-autoimmune cohort. There were no

15264610, 0, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.70086 by Universidad De Zaragoza, Wiley Online Library on [07/04/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Demographic characteristics of the patients with and without autoimmune diseases included in the study.

Variables	All, $n=388$	No AD, $n=194$	AD, $n=194$	p value (unadjusted)
Age, years, mean (SD)	49.3 (10.2)	49.4 (10.1)	49.2 (10.3)	0.881
Sex, female, *n* (%)	360 (92.8)	180 (92.8)	180 (92.8)	0.999
High blood pressure, *n* (%)	56 (14.4)	31 (16.0)	25 (12.9)	0.470
Dyslipidemia, *n* (%)	59 (15.2)	31 (16)	28 (14.4)	0.777
Diabetes mellitus, *n* (%)	9 (2.3)	4 (2.1)	5 (2.3)	0.999
Active smoking, *n* (%)	74 (19.1)	31 (16)	43 (22.2)	0.155
Alcohol consumption, *n* (%)	4 (1)	4 (2.1)	0 (0)	0.123
Anxiety, *n* (%)	152 (39.2)	67 (34.5)	85 (43.8)	0.077
Depression, *n* (%)	139 (35.8)	57 (29.4)	82 (42.3)	0.011*
Insomnia, *n* (%)	117 (30.2)	57 (29.5)	60 (30.9)	0.851
Chronic migraine, *n* (%)	316 (81.4)	153 (78.9)	163 (84.0)	0.240
Migraine with aura, *n* (%)	104 (26.9)	54 (27.8)	50 (26.0)	0.778
Time with migraine, years mean (SD)	28.3 (13)	29.7 (12.7)	26.9 (13.3)	0.042*
Time with chronic migraine, months mean (SD)	10.9 (9.9)	12.2 (10.9)	9.66 (8.6)	0.022*
Medication overuse, *n* (%)	254 (65.8)	118 (60.8)	136 (70.8)[a]	0.049*
No. of prior preventive treatments, mean (SD)	5.4 (2.5)	5.13 (2.3)	5.66 (2.7)	0.041*

Abbreviations: AD, autoimmune disease; SD, standard deviation.

[a]Data were complete for all baseline variables except medication overuse for which data were available for 192 patients in this group.

*$p<0.05$.

TABLE 2 Autoimmune disease type among patients with AD and CGRP monoclonal antibodies.

Autoimmune disease type	$n=194$
Rheumatological, *n* (%)	68 (35)
Hyper/hypothyroidism, *n* (%)	49 (25)
Gastrointestinal, *n* (%)	37 (19)
Neurological, *n* (%)	22 (11)
Autoimmune-linked hypersensitivity syndromes, *n* (%)	9 (5)
Dermatological, *n* (%)	8 (4)
Diabetes mellitus type 1, *n* (%)	2 (1)

Abbreviations: AD, autoimmune disease; CGRP, calcitonin gene-related peptide.

differences in the prevalence of vascular risk factors or lifestyle factors between groups. Regarding psychiatric comorbidities, depression showed significantly higher rates in the AD group (42.3% vs. 29.4%; $p=0.011$), although anxiety (43.8% vs. 34.5%; $p=0.077$) and insomnia (30.9% vs. 29.5%; $p=0.851$) were no different. Chronic migraine (84% vs. 78.9%; $p=0.240$) and migraine with aura (26% vs. 27.8%; $p=0.778$) were common, with the autoimmune group reporting a shorter duration of chronic migraine (9.66 months vs. 12.2 months; $p=0.022$) and a higher rate of medication overuse (71% vs. 61%; $p=0.049$). Additionally, the AD group had had higher preventive treatments on average (mean, 6 [SD, 3] vs. 5 [SD, 3]; $p=0.041$). Among patients with AD, there were 24 of 194 (12.4%) of patients receiving other monoclonal antibodies. All demographic variables are included in Table 1.

Effectiveness in patients under anti-CGRP therapies with and without autoimmune disorders

Patients with AD had a significantly lower proportion of patients achieving ≥50% response rate in MMD at 3 months (46% vs. 58%; $p=0.006$), 6 months (53% vs. 69%; $p=0.006$), and 9 months (52% vs. 74%; $p=0.006$) compared to patients without AD (Table 3). Patients achieving ≥50% response rate in MHD, MMD, and MHD in which the group (no AD vs. AD)-by-time interaction did not show statistically significant differences and therefore it was not included in the final GEE models, showed a worse response in patients with AD compared to patients without AD independent of the presence of depression and medication overuse (Figure 1; Tables 4, 1S, 2S, 3S, and 4S).

Safety in patients with and without autoimmune disorders

The overall presence of treatment emerging adverse events was similar between the two groups. Among patients with AD, we observed a temporary AD-related worsening in 22 patients (11.5%) at mean 5.7 (SD, 10) months, but only one patient stopped treatment due to the worsening of the disease with a

15264610, 0, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.70086 by Universidad De Zaragoza, Wiley Online Library on [07/04/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 Effectiveness measured by ≥50% response rates in patients with and without ADs.

Effectiveness	No AD ($n=194$)	AD ($n=194$)	p value (adjusted)
≥50% response in MMD at 3 months, *n* (%)	175 (58.3)	180 (46.1)	0.006**
≥50% response in MHD at 3 months, *n* (%)	176 (50.0)	182 (41.2)	0.035**
≥50% response in MMD at 6 months, *n* (%)	165 (68.5)	153 (52.9)	0.006**
≥50% response in MHD at 6 months, *n* (%)	164 (59.1)	156 (48.7)	0.035*
≥50% response in MMD at 9 months, *n* (%)	105 (74.3)	105 (52.4)	0.006**
≥50% response in MHD at 9 months, *n* (%)	105 (75.0)	109 (53.2)	0.035*
≥50% response in MMD at 12 months, *n* (%)	115 (67.8)	104 (56.7)	0.006**
≥50% response in MHD at 12 months, *n* (%)	112 (66.1)	105 (50.5)	0.035*

Note: Adjusted p values (*) are derived from Bonferroni-corrected post hoc comparisons across time points based on GEE models with ≥50% response rates in MHD or MMD as the dependent variable and depression, medication overuse, and autoimmune disease included as covariates.

Abbreviations: AD, autoimmune disease; GEE, generalized estimating equation; MHD, monthly headache days; MMD, monthly migraine days.

*$p<0.05$. **$p<0.01$.

following improvement. Treatment emerging adverse events in patients with and without AD are included in Table 5.

Variables associated with migraine in patients with autoimmune disorders

A multivariable logistic regression analysis found that medication overuse was independently associated with higher odds of AD (odds ratio [OR], 2.90; 95% confidence interval [CI], 1.32–6.56; $p=0.009$), whereas achieving a ≥50% response in MMD at 9 months was independently associated with lower odds of AD (OR, 0.32; 95% CI, 0.15–0.68; $p=0.004$). In addition, longer duration of chronic migraine was independently associated with lower odds of AD (OR, 0.94 per year; 95% CI, 0.90–0.97; $p=0.002$) (Table 5S). The model showed good calibration according to the Hosmer–Lemeshow test ($\chi^2=7.15$; $df=8$; $p=0.521$).

DISCUSSION

In this age- and sex-matched cohort study, we evaluated sociodemographic, migraine-related, effectiveness, and safety variables between patients with and without AD undergoing anti-CGRP therapies by contributing valuable insights to the limited existing literature on this topic.

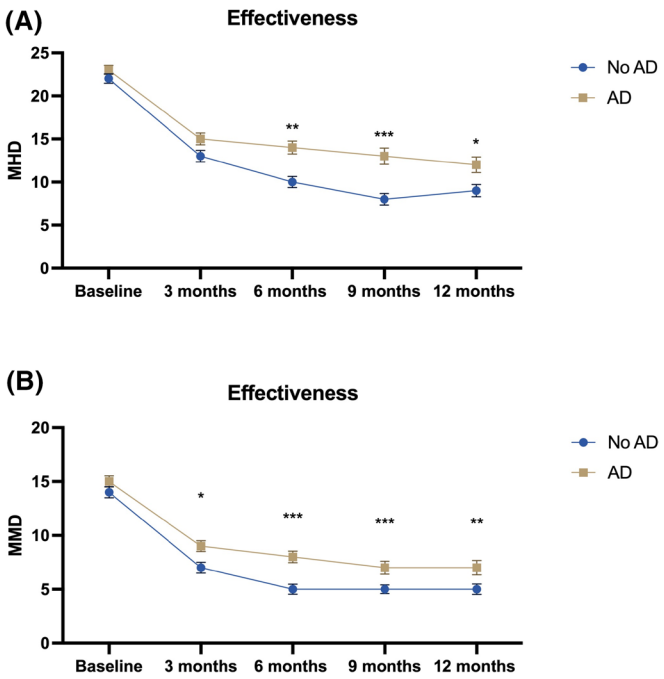

FIGURE 1 Effectiveness of anti-CGRP therapies in patients with and without autoimmune disorders. (A) Response in MHD. (B) Response in MMD. Error bars represent the SEM. Adjusted p values (*$p<0.05$; **$p<0.01$; ***$p<0.001$) correspond to Bonferroni-corrected post hoc comparisons. AD, autoimmune diseases; CGRP, calcitonin gene-related peptide; MHD, monthly headache days; MMD, monthly migraine days; SEM, standard errors of the mean.

15264610, 0, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.70086 by Universidad De Zaragoza, Wiley Online Library on [07/04/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 4 GEE model evaluating the ≥50% response rate in MMD across multiple time points.

Variables	aORs	95% CI lower	95% CI upper	*p* value (adjusted)
≥50% RR MMD 3 months	Ref			
≥50% RR MMD 6 months	1.34	1.09	1.66	0.004**
≥50% RR MMD 9 months	1.37	1.01	1.86	0.027*
≥50% RR MMD 12 months	1.31	0.95	1.81	0.088
AD	0.61	0.44	0.85	0.006**
Depression	0.56	0.40	0.80	0.003**
Medication overuse	0.69	0.48	0.99	0.046*

Note: The model included the ≥50% response rate in MMD as the dependent variable and autoimmune disease, depression, and medication overuse as covariates. Results are reported as aORs. $N = 374$ patients; 1098 observations.

Abbreviations: AD, autoimmune disease; aOR, adjusted odds ratio; CI, confidence interval; GEE, generalized estimating equation; MMD, monthly migraine days.

*$p < 0.05$. **$p < 0.01$.

TABLE 5 Treatment emerging AEs in patients with and without ADs.

Treatment emerging AEs	No AD, $n = 194$	AD, $n = 194$	*p* value (unadjusted)
Adverse events, *n* (%)	66 (34)	73 (37.7)	0.575
Constipation, *n* (%)	34 (17.5)	38 (19.6)	0.732
Injection site reaction, *n* (%)	27 (13.9)	16 (8.2)	0.087
Dizziness, *n* (%)	18 (9.3)	22 (11.3)	0.655
Fatigue, *n* (%)	4 (2.1)	9 (4.6)	0.259
High blood pressure, *n* (%)	4 (2.1)	2 (1)	0.685
Nausea, *n* (%)	3 (1.5)	2 (1)	0.683
Vertigo, *n* (%)	2 (1)	2 (1)	0.999
Headache, *n* (%)	3 (1.5)	2 (1)	0.999
Alopecia, *n* (%)	3 (1.5)	1 (0.5)	0.623
Allergies, *n* (%)	2 (1)	3 (1.5)	0.999
Flulike symptoms, *n* (%)	1 (0.5)	3 (1.5)	0.623
Changes in weight, *n* (%)	1 (0.5)	1 (0.5)	0.999
Arthralgia, *n* (%)	1 (0.5)	1 (0.5)	0.999
Infection, *n* (%)	0 (0)	1 (0.5)	0.999
Fever, *n* (%)	0 (0)	2 (1)	0.499
Stroke, *n* (%)	0 (0)	1 (0.5)	0.999

Note: Values are *n* (% of patients). Percentages are calculated using the total number of patients in each group ($n = 194$). Patients may have experienced more than one adverse event.

Abbreviations: AD, autoimmune disease; AEs, adverse events.

Demographic and clinical characteristics

A key finding of this study was the elevated prevalence of depression in the AD group, underscoring the complex relationship between depression and migraine. In this study, 35.8% of all participants reported depression, with a higher prevalence in the AD group compared to patients without AD.

This aligns with evidence linking chronic inflammation and depression through pathways such as cytokine-induced neuroinflammation, hypothalamic–pituitary–adrenal axis dysregulation, and neurotransmitter alterations.[23] In line with these findings, recent evidence shows a higher rate of depression in females within the first 5 years of MS diagnosis compared to those without it.[16] Depression in AD is particularly concerning, as it may worsen disease activity and affect treatment outcome. Importantly, depression can also negatively influence AD activity, amplify inflammatory markers, and worsen conditions such as chronic migraine.[5,24,25] In turn, this creates a vicious cycle, where worsening physical symptoms contribute to heightened psychological distress, perpetuating the disease burden. The observed association between depression and migraine severity in this study underscores the importance of recognizing and addressing mental health as a key component of comprehensive care in patients with AD.[26] This includes regular screening for depression, offering psychological support, and considering multidisciplinary approaches that combine medical, psychological, and social care.[27,28] Addressing depression may also enhance overall quality of life for this vulnerable population treated with the new anti-CGRP therapies.[29] Future research should explore the bidirectional relationship between depression and AD further, particularly focusing on the potential benefits of targeted interventions such as anti-inflammatory treatments or tailored psychotherapies in mitigating both depressive symptoms and disease progression in patients with migraine and AD.

Additionally, the higher prevalence of medication overuse and the reduced response to treatment—as reflected by a lower number of patients achieving a ≥50% response rate in MMD—despite a shorter chronic migraine duration, suggest a more challenging and possibly treatment-resistant clinical profile in patients with AD. This pattern may reflect the interplay between chronic migraine and immune dysregulation, as autoimmune processes have been shown to exacerbate central sensitization and chronic pain syndromes, ultimately complicating migraine management due to the interplay between chronic migraine and underlying autoimmune conditions.[30,31] Moreover, the connection between inflammatory, immunological, and vascular processes shared both by migraine and AD has been increasingly evident through the years.[5]

15264610, 0, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.70086 by Universidad De Zaragoza, Wiley Online Library on [07/04/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Treatment effectiveness

Patients with AD demonstrated a reduced response to anti-CGRP therapies compared to patients without AD. In particular, in later stages of patients' follow-up, patients without AD achieved significantly higher rates of ≥50% response to treatment, suggesting a more robust therapeutic effect in this group.

In contrast, the comparatively diminished response observed in patients with AD may reflect a more chronic and treatment-resistant migraine phenotype. Furthermore, systemic inflammation and immune dysregulation—hallmarks of AD—may interfere with migraine-specific mechanisms and reduce responsiveness to targeted therapies therefore making AD a poor prognostic factor. Despite this, the effectiveness observed in the AD group still aligns with that reported in real-world studies, supporting the continued clinical value of anti-CGRP therapies in this population, with similar to the responses observed in other AD such as multiple sclerosis or inflammatory bowel disease.[18,20,32]Additionally, this group showed higher rates of medication overuse which is associated with poorer treatment outcomes. Importantly, recent evidence indicates that earlier initiation of anti-CGRP therapy is linked to improved clinical response, which could partly explain the suboptimal results in this subgroup.[33]

Safety and tolerability

The overall rate of adverse events was comparable between groups; however, injection site reactions were more frequent among patients without AD. This improvement may reflect enhanced management of anti-CGRP drugs, which are mainly administered subcutaneously, through strategies learned from treating AD and/or the immunosuppressive or immunomodulatory effect of these drugs.[34–36]

Regarding the influence of anti-CGRP on the AD evolution, recent studies have demonstrated a bidirectional relation between migraine and rheumatoid arthritis,[9] with a higher migraine risk in this population regardless of serum antibody titration[11] or blood C-reactive protein levels.[13] Moreover, some publications show a higher prevalence of migraine among adults with IBD.[17] Besides that, plasma CGRP levels have been associated with sustained hyperinflammation in infectious conditions such as COVID-19.[37] Furthermore, it has been reported that the presence of immunorheumatological comorbidities may have a negative impact on the response to anti-CGRP treatment.[38] However, current evidence regarding the effectiveness and security analysis of anti-CGRP drugs in patients with multiple sclerosis treated with disease-modifying medication has shown that anti-CGRP therapy treatment did not increase the frequency of multiple sclerosis outbreaks or infections after 18 months of follow-up.[20]

In this study, worsening symptoms were observed in 22 patients (11.5%) with AD. Importantly, only one patient required treatment discontinuation due to these symptoms, whereas the remaining patients were able to continue anti-CGRP therapy without modification and subsequently stabilized. These results support the overall safety profile of anti-CGRP therapies in patients with AD and suggest that their use may be considered under appropriate clinical monitoring. Although a subset of patients may experience transient disease activation—as previously reported[39,40]—these events appear to be manageable. Further research is needed to clarify the mechanisms underlying poorer responses to anti-CGRP therapies in patients with AD and to assess long-term efficacy and safety.[41]

Limitations

Among the limitations of this study, it should be noted that due to reimbursement criteria, our population primarily consisted of patients with high-frequency episodic migraine and chronic migraine who did not receive benefit from several preventive treatments. Although this limits the generalizability to all patients with migraine, it reflects the typical population seen in headache clinics, thereby increasing the relevance of our findings to real-world clinical practice. We also acknowledge that changes in other preventive medications, such as dose adjustments or treatment switching during follow-up, were not systematically recorded or controlled for, and the absence of validated scales for depression, disability, and other variables not included in this study may have influenced treatment responses; however, these factors are not routinely assessed in standard clinical settings. It would be inequitable to exclude such individuals from access to therapy. Additionally, as a real-world observational cohort, follow-up data were not available for all patients at later time points, which may introduce attrition-related bias and potentially inflate long-term effectiveness estimates. To address this, longitudinal analyses were conducted using GEE models, which allow inclusion of all available observations and appropriately account for repeated measures over time; however, residual bias related to loss to follow-up cannot be fully excluded. Additionally, analyzing systemic and/or local inflammatory diseases as a combined group, reflecting real-world clinical practice, allowed us to identify a distinct treatment response pattern. However, heterogeneous inflammatory diseases were grouped together, and further specifically designed subgroup studies are needed to elucidate disease-specific characteristics. Therefore, findings should be interpreted at a group level, and further studies focusing on specific AD subtypes are needed to better define differential treatment responses. Overall, our approach seeks to offer insights that may support broader improvements in migraine care.

Implications for clinical practice and future directions

Collectively, these findings advocate for tailored approaches to managing migraine in patients with AD, including adjunctive immunomodulatory therapies and multidisciplinary care. Our findings suggest

15264610, 0, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.70086 by Universidad De Zaragoza, Wiley Online Library on [07/04/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

that integrating mental health interventions, addressing medication overuse early, and tailoring preventive treatments may enhance outcomes in this population. Future research should explore the role of targeted immunomodulatory strategies, anti-inflammatory therapies, and tailored psychotherapies in improving both migraine outcomes and quality of life for patients with AD. Additionally, further investigation into the mechanisms underlying reduced treatment effectiveness in autoimmune populations is warranted to guide the development of more effective therapeutic approaches.[42]

CONCLUSIONS

This study provides critical insights into the interplay between migraine and AD, comparing treatment effectiveness and safety outcomes in patients receiving anti-CGRP therapies. Our findings suggest that although anti-CGRP therapies remain effective and generally safe under active monitoring for potential symptom worsening, patients with AD exhibit diminished treatment response and more complex clinical profiles. These results highlight the importance of early intervention and tailored therapeutic strategies including collaboration between neurologists and immunologists to improve outcomes.

AUTHOR CONTRIBUTIONS

María Clara García-Castillo: Investigation; writing – original draft; data curation; validation; formal analysis. **Álvaro Sierra-Mencía:** Investigation; data curation; validation. **Edoardo Caronna:** Investigation; data curation; validation. **Daniel Toledo-Alfocea:** Investigation; validation; data curation. **Alex Jaimes:** Investigation; validation; data curation. **Sarai Urtiaga:** Investigation; validation; data curation. **Javier Casas-Limón:** Investigation; validation; data curation. **Albert Muñoz-Vendrell:** Investigation; validation; data curation. **Sonia Santos-Lasaosa:** Investigation; validation; data curation. **Valvanuz García Martín:** Investigation; validation; data curation. **Guillermo Martín Ávila:** Investigation; validation; data curation. **Marcos Polanco:** Investigation; validation; data curation. **Maria Dolores Villar-Martínez:** Investigation; validation; data curation. **Cristina Trevino-Peinado:** Investigation; validation; data curation. **Laura Rubio-Flores:** Investigation; validation; data curation. **Antonio Sánchez-Soblechero:** Investigation; validation; data curation. **Leonardo Portocarrero Sánchez:** Investigation; validation; data curation. **Elisa Luque-Buzo:** Investigation; validation; data curation. **Alberto Lozano-Ros:** Investigation; validation; data curation. **Ana Beatriz Gago-Veiga:** Data curation. **Javier Díaz-De-Terán:** Investigation; validation; data curation. **Andrea Recio García:** Investigation; validation; data curation. **Javiera Canales Rodríguez:** Investigation; validation; data curation. **Andrea Gómez García:** Investigation; validation; data curation. **Marta González Salaices:** Investigation; validation; data curation. **Sergio Campoy:** Investigation; validation; data curation. **Ane Mínguez-Olaondo:** Investigation; validation; data curation. **Stefania Maniataki:** Investigation; validation; data curation. **Vicente González-Quintanilla:** Data curation; validation; investigation. **Jesús Porta-Etessam:** Investigation; validation; data curation. **María-Luz Cuadrado:** Investigation; validation; data curation. **Ángel Luis Guerrero Pera:** Investigation, validation and data curation. **Patricia Pozo-Rosich:** Investigation; validation; data curation. **Jaime Rodríguez-Vico:** Investigation; validation; data curation. **Mariano Huerta-Villanueva:** Investigation; validation; data curation. **Julio Pascual:** Investigation; validation; data curation. **Peter J. Goadsby:** Investigation; validation; data curation. **Alicia Gonzalez-Martinez:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; visualization; writing – review and editing; software; formal analysis; project administration; data curation; supervision; resources.

AFFILIATIONS

[1]Facultad de Medicina, Universidad Autónoma de Madrid (UAM), Madrid, Spain

[2]Neurology and Immunology Department, Hospital Universitario de la Princesa, Madrid, Spain

[3]Headache Unit, Neurology Department, Hospital Clínico Universitario de Valladolid, Valladolid, Spain

[4]Health Research Institute of Valladolid (IBioVALL), Valladolid, Spain

[5]Headache Clinic, Neurology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[6]Headache and Neurological Pain Research Group, Vall d'Hebron Research Institute, Barcelona, Spain

[7]Servicio de Neurología, Hospital 12 Octubre, Madrid, Spain

[8]Headache Unit, Neurology Department, Fundación Jiménez Díaz University Hospital, Madrid, Spain

[9]Neurology Department, Hospital de Torrejón, Madrid, Spain

[10]Headache Unit, Neurology Department, Hospital Universitario Fundación Alcorcón, Alcorcón, Spain

[11]Headache Unit, Neurology Department, Hospital Universitari de Bellvitge-IDIBELL, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

[12]Neurology Department, Hospital Universitario Lozano Blesa, IIS Aragon, University of Zaragoza, Zaragoza, Spain

[13]Instituto de Investigación Sanitaria (IIS) Biogipuzkoa, San Sebastián, Spain

[14]Neurology Department, Hospital de Getafe, Getafe, Spain

[15]Service of Neurology, University Hospital Marqués de Valdecilla, Universidad de Cantabria and IDIVAL, Santander, Spain

[16]NIHR King's Clinical Research Facility, Wolfson SPaRC, King's College London, London, UK

[17]Headache Clinic, Neurology Department, Severo Ochoa University Hospital, Leganés, Spain

[18]Headaches, Craniofacial Pain and Neurological Pain Unit, Vithas Clinical Neuroscience Institute, La Milagrosa, Aravaca, Vithas Hospitals Group, Arturo Soria University Hospitals, Madrid, Spain

[19]Neurology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[20]Neurology Department, Hospital Universitario de la Paz, Madrid, Spain

15264610, 0, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.70086 by Universidad De Zaragoza, Wiley Online Library on [07/04/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[21]Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Madrid, Spain
[22]Headache Unit, Hospital Universitario de la Princesa, Madrid, Spain
[23]Neurology Department, Pontificia Universidad Catolica de Chile, Hospital Biprovincial Quillota Petorca, Quillota, Chile
[24]Headache Unit, Hospital Universitari de Bellvitge & Hospital de Viladecans – IDIBELL, Universitat de Barcelona, Barcelona, Spain
[25]Neurology Department, Hospital Universitario Donostia-Osakidetza, Neuroscience Area, Biogipuzkoa Health Institute, Donostia, Spain
[26]Department of Medicine, University of Deusto, Bilbao, Spain
[27]Department of Physical Therapy, Faculty of Health Sciences, University of Deusto, San Sebastian, Spain
[28]Neuroscience Area, Faculty of Biomedical and Health Sciences, Alfonso X el Sabio University, Madrid, Spain
[29]School of Medicine, Universidad Complutense de Madrid, Department of Neurology, Hospital Clínico San Carlos, Madrid, Spain
[30]Departamento de Medicina, Universidad de Valladolid, Valladolid, Spain
[31]Division of Biomedical Sciences, King Abdullah University of Science and Technology, Thuwal, Saudi Arabia

ACKNOWLEDGMENTS

This work was funded by the Instituto de Salud Carlos III, (ISCIII), grant number JR23/00005 and PI24/01085, and co-funded by the European Union (FEDER/European Regional Development Fund-"A way to make Europe"). We gratefully acknowledge the patients and the scientific community for their invaluable support. We also thank the European Headache Federation for the award for best poster at the European Headache Federation Congress 2024 held in Rotterdamm, NL, December 4–7, 2024.

FUNDING INFORMATION

This work was supported by the Instituto de Salud Carlos III (JR23/00005 and PI24/01085) and co-funded by the European Union (FEDER/European Regional Development Fund-"A way to make Europe").

CONFLICT OF INTEREST STATEMENT

Edoardo Caronna has received honoraria from Novartis, Chiesi, Lundbeck, MedScape, Lilly, TEVA, Dr. Reddy's, and Organon; his salary has been partially funded by Río Hortega grant Acción Estratégica en Salud 2017–2020 from Instituto de Salud Carlos III (CM20/00217) and Juan Rodés fellowship, Subprograma Estatal de Incorporación de la Acción Estratégica en Salud 2023 (JR23/00065). He is a junior editor for Cephalalgia. **Alex Jaimes** has received honoraria from Lilly, TEVA, Lundbeck, and AbbVie. **Albert Muñoz-Vendrell** has received honoraria from AbbVie, Amgen, Biogen, Bial, Chiesi, Janssen, Kern Pharma, Lilly, Lundbeck, Merck, Novartis, Organon, Pfizer, Roche, Sanofi, Teva, UCB, and Zambon. **Antonio Sánchez-Soblechero** has received fees from TEVA for sponsored lectures. **Ana Beatriz Gago-Veiga** has received speaker honoraria and/or clinical advisor from Novartis, Lilly, TEVA, Exeltis, Chiesi, AbbVie, Pfizer, Dr. Reddy's, and Lundbeck. **María-Luz Cuadrado** has been involved as a consultant or lecturer for AbbVie, Chiesi, Lundbeck, Novartis, and Teva. **Ángel Luis Guerrero Peral** has participated in Advisory Boards: AbbVie, Elly Lilly, Lundbeck, Organon, Pfizer, and TEVA. Speaker boards: AbbVie, Elly Lilly, Exeltis, Lundbeck, and TEVA. **Mariano Huerta-Villanueva** received honoraria for participating on advisory boards and for collaborations as consultant, scientific communications, speaker, research support as well as funding for travel and congress attending expenses from AbbVie, Novartis, Lilly, TEVA, Lundbeck, Dr. Reddy's, Pfizer, Almirall, Chiesi, Esai, Kern Pharma, and Zambon. **Patricia Pozo-Rosich** has received, in the last 3 years, honoraria as a consultant and speaker from AbbVie, Amgen, Dr. Reddy's, Eli Lilly, Lundbeck, Medscape, Novartis, Organon, Pfizer, and Teva Pharmaceuticals. Her research group has received research grants from AbbVie, AGAUR, EraNet Neuron, FEDER RIS3CAT, Instituto Investigación Carlos III, MICINN, Novartis, and Teva Pharmaceuticals, and has received funding for clinical trials from AbbVie, Amgen, Biohaven, Eli Lilly, Lundbeck, Novartis, Pfizer, and Teva Pharmaceuticals. She is the founder of www.midolordecabeza.org. Patricia Pozo-Rosich does not own stocks from any pharmaceutical company. **Peter J. Goadsby** reports, over the last 36 months, personal fees for consulting from AbbVie, CoolTech LLC, Dr. Reddy's, Epalex, Ipsen, Kallyope, Linpharma, Lundbeck, Orion Pharma, Pfizer, PureTech Health LLC, Satsuma, Scilex Pharmaceuticals, Seaport Therapeutics, Septurna, and Teva Pharmaceuticals, personal fees for advice through Gerson Lehrman Group, Guidepoint, and SAI Med Partners, fees for educational materials from CME Outfitters and WebMD, and publishing royalties or fees from Massachusetts Medical Society, Oxford University Press, UptoDate, and Wolters Kluwer. **Alicia Gonzalez-Martinez** has received speaker honoraria from TEVA, Lilly, and Altermedica. Her salary has been partially funded by Río Hortega grant Acción Estratégica en Salud from Instituto de Salud Carlos III (CM21/00178) and Juan Rodés fellowship, Subprograma Estatal de Incorporación de la Acción Estratégica en Salud 2023 (JR23/00005). **Javier Casas-Limón** has received speaker and consulting fees from AbbVie, Almirall, Bial, Chiesi, Italfarmaco, KRKA, Lilly, Lundbeck, Novartis, Organon, Pfizer, Teva, and UCB. **Jaime Rodríguez-Vico** has received speaker and consulting fees from Teva, Lilly, Novartis, AbbVie, Pfizer, Dr. Reddy's, and Exeltis. **María Clara García-Castillo, Álvaro Sierra-Mencía, Daniel Toledo-Alfocea**, **Sarai Urtiaga**, **Valvanuz García Martín**, **Guillermo Martín Ávila**, **Marcos Polanco**, **Maria Dolores Villar-Martínez**, **Cristina Trevino-Peinado**, **Laura Rubio-Flores**, **Leonardo Portocarrero Sánchez**, **Elisa Luque-Buzo**, **Alberto Lozano-Ros**, **Javier Díaz-De-Terán**, **Andrea Recio García**, **Javiera Canales Rodríguez**, **Andrea Gómez García**, **Marta González Salaices**, **Sergio Campoy**, **Ane Mínguez-Olaondo**, **Stefania Maniataki**, **Vicente González-Quintanilla**, **Jesús Porta-Etessam, Sonia Santos-Lasaosa** and **Julio Pascual** declare that they have no competing interest regarding the present manuscript.

15264610, 0, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.70086 by Universidad De Zaragoza, Wiley Online Library on [07/04/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

DATA AVAILABILITY STATEMENT

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

María Clara García-Castillo https://orcid.org/0009-0005-4905-4186
Álvaro Sierra-Mencía https://orcid.org/0000-0002-0022-6064
Edoardo Caronna https://orcid.org/0000-0001-5525-0267
Daniel Toledo-Alfocea https://orcid.org/0000-0003-3651-1614
Alex Jaimes https://orcid.org/0000-0002-0890-9484
Javier Casas-Limón https://orcid.org/0000-0002-7353-4084
Albert Muñoz-Vendrell https://orcid.org/0000-0001-8221-865X
Sonia Santos-Lasaosa https://orcid.org/0000-0002-4141-7705
Marcos Polanco https://orcid.org/0009-0006-8609-7385
Maria Dolores Villar-Martínez https://orcid.org/0000-0003-3920-0176
Cristina Trevino-Peinado https://orcid.org/0000-0001-8711-4884
Laura Rubio-Flores https://orcid.org/0000-0001-5570-8055
Antonio Sánchez-Soblechero https://orcid.org/0000-0002-7098-8494
Alberto Lozano-Ros https://orcid.org/0000-0002-5186-8657
Ana Beatriz Gago-Veiga https://orcid.org/0000-0002-0038-3406
Javier Díaz-De-Terán https://orcid.org/0000-0003-0064-6269
Andrea Recio García https://orcid.org/0009-0007-4980-4797
Sergio Campoy https://orcid.org/0000-0002-8135-4139
Ane Mínguez-Olaondo https://orcid.org/0000-0002-7742-3920
Vicente González-Quintanilla https://orcid.org/0000-0003-0902-3906
Jesús Porta-Etessam https://orcid.org/0000-0002-7034-682X
María-Luz Cuadrado https://orcid.org/0000-0001-8246-3743
Ángel Luis Guerrero Peral https://orcid.org/0000-0001-7493-6002
Patricia Pozo-Rosich https://orcid.org/0000-0003-0796-4702
Jaime Rodríguez-Vico https://orcid.org/0000-0001-9360-5444
Mariano Huerta-Villanueva https://orcid.org/0000-0003-0181-5335
Julio Pascual https://orcid.org/0000-0002-3189-7573
Peter J. Goadsby https://orcid.org/0000-0003-3260-5904
Alicia Gonzalez-Martinez https://orcid.org/0000-0002-1228-1503

REFERENCES

1. Steiner TJ, Stovner LJ. Global epidemiology of migraine and its implications for public health and health policy. *Nat Rev Neurol*. 2023;19(2):109-117.
2. Ferrari MD, Goadsby PJ, Burstein R, et al. Migraine. *Nat Rev Dis Primers*. 2022;8(1):1-20.
3. Ray JC, Allen P, Bacsi A, et al. Inflammatory complications of CGRP monoclonal antibodies: a case series. *J Headache Pain*. 2021;22(1):121.
4. Serrano Hernández A. Células colaboradoras (TH1, TH2, TH17) y reguladoras (Treg, TH3, NKT) en la artritis reumatoide. *Reumatol Clin*. 2009;5:1-5.
5. Peroutka SJ. Neurogenic inflammation and migraine: implications for the therapeutics. *Mol Interv*. 2005;5(5):304-311.
6. Salahi M, Parsa S, Nourmohammadi D, et al. Immunologic aspects of migraine: a review of literature. *Front Neurol*. 2022;13:944791.
7. Straburzyński M, Kopyt D, Marschollek K, et al. Increased infection risk in patients on preventive CGRP-targeting therapies- a meta-analysis and clinical effect assessment. *J Headache Pain*. 2025;26(1):88.
8. Holzmann B. Antiinflammatory activities of CGRP modulating innate immune responses in health and disease. *Curr Protein Pept Sci*. 2013;14(4):268-274.
9. Kim YH, Lee JW, Kim Y, et al. Bidirectional association between migraine and rheumatoid arthritis: two longitudinal follow-up studies with a national sample cohort. *BMJ Open*. 2021;11(6):e046283.
10. Moisset X, Giraud P, Dallel R. Migraine in multiple sclerosis and other chronic inflammatory diseases. *Rev Neurol (Paris)*. 2021;177(7):816-820.
11. Kang S, Eun Y, Han K, et al. Heightened migraine risk in patients with rheumatoid arthritis: a national retrospective cohort study. *Headache*. 2025;65(2):326-337.
12. Mohammadi M, Kankam SB, Salehi S, et al. The association between multiple sclerosis and migraine: a meta-analysis. *Mult Scler Relat Disord*. 2023;79:104954.
13. Mathieu S, Couderc M, Pereira B, et al. Prevalence of migraine and neuropathic pain in rheumatic diseases. *J Clin Med*. 2020;9(6):1890.
14. Moisset X, Ouchchane L, Guy N, Bayle DJ, Dallel R, Clavelou P. Migraine headaches and pain with neuropathic characteristics: comorbid conditions in patients with multiple sclerosis. *Pain*. 2013;154(12):2691-2699.
15. Mirmosayyeb O, Barzegar M, Nehzat N, Shaygannejad V, Sahraian MA, Ghajarzadeh M. The prevalence of migraine in multiple sclerosis (MS): a systematic review and meta-analysis. *J Clin Neurosci*. 2020;79:33-38.
16. Eid K, Torkildsen Ø, Aarseth J, et al. Migraine in the multiple sclerosis prodrome: a prospective nationwide cohort study in pregnant women. *J Headache Pain*. 2024;25(1):225.
17. Liu Y, Xu F, Wheaton AG, Greenlund KJ, Thomas CW. The association between inflammatory bowel disease and migraine or severe headache among US adults: findings from the National Health Interview Survey, 2015-2016. *Headache*. 2021;61(4):612-619.
18. Gonzalez-Martinez A, Muro I, Quintas S, et al. Headache in patients with inflammatory bowel disease: Migraine prevalence according to the Migraine Screening-Questionnaire (MS-Q) and headache characteristics. *Gastroenterol Hepatol*. 2024;47(1):63-71.
19. Pascual-Mato M, Gárate G, de Prado-Tejerina C, et al. Increased prevalence of migraine in women with inflammatory bowel disease: a cross-sectional study. *Cephalalgia*. 2024;44(3):3331024241233979.
20. Gonzalez-Martinez A, Bose G, Chitnis T. Anti-CGRP therapies for migraine in multiple sclerosis patients. *Mult Scler*. 2022;28(13):2149-2150.
21. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
22. Sacco S, Amin FM, Ashina M, et al. European headache federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update. *J Headache Pain*. 2022;23(1):67.
23. Troubat R, Barone P, Leman S, et al. Neuroinflammation and depression: a review. *Eur J Neurosci*. 2021;53(1):151-171.
24. Polityńska B, Pokorska O, Wojtukiewicz AM, et al. Is depression the missing link between inflammatory mediators and cancer? *Pharmacol Ther*. 2022;240:108293.
25. Levy D. Migraine pain, meningeal inflammation, and mast cells. *Curr Pain Headache Rep*. 2009;13(3):237-240.
26. Loggia ML. «Neuroinflammation»: does it have a role in chronic pain? Evidence from human imaging. *Pain*. 2024;165(11S):S58-S67.

15264610, 0, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.70086 by Universidad De Zaragoza, Wiley Online Library on [07/04/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

27. Falla K, Kuziek J, Mahnaz SR, Noel M, Ronksley PE, Orr SL. Anxiety and depressive symptoms and disorders in children and adolescents with migraine: a systematic review and meta-analysis. *JAMA Pediatr*. 2022;176(12):1176-1187.
28. Irimia P, Garrido-Cumbrera M, Santos-Lasaosa S, et al. Impact of monthly headache days on anxiety, depression and disability in migraine patients: results from the Spanish atlas. *Sci Rep*. 2021;11(1):8286.
29. Torres-Ferrús M, Gallardo VJ, Alpuente A, Caronna E, Giné-Ciprés E, Pozo-Rosich P. Improvement of migraine depressive symptoms is not related to headache frequency: exploring the impact of anti-CGRP therapies. *Cephalalgia*. 2024;44(2):3331024231222923.
30. Goebel A, Andersson D, Helyes Z, Clark JD, Dulake D, Svensson C. The autoimmune aetiology of unexplained chronic pain. *Autoimmun Rev*. 2022;21(3):103015.
31. Lacagnina MJ, Heijnen CJ, Watkins LR, Grace PM. Autoimmune regulation of chronic pain. *Pain Rep*. 2021;6(1):e905.
32. Gonzalez-Martinez A, Pagán J, Sanz-García A, et al. Machine-learning-based approach for predicting response to anti-calcitonin gene-related peptide (CGRP) receptor or ligand antibody treatment in patients with migraine: a multicenter Spanish study. *Eur J Neurol*. 2022;29(10):3102-3111.
33. Caronna E, Gallardo VJ, Egeo G, et al. Redefining migraine prevention: early treatment with anti-CGRP monoclonal antibodies enhances response in the real world. *J Neurol Neurosurg Psychiatry*. 2024;95(10):927-937.
34. Raffaelli B, Fitzek M, Overeem LH, Storch E, Terhart M, Reuter U. Clinical evaluation of super-responders vs. non-responders to CGRP(−receptor) monoclonal antibodies: a real-world experience. *J Headache Pain*. 2023;24(1):16.
35. Raffaelli B, Terhart M, Overeem LH, et al. Migraine evolution after the cessation of CGRP(−receptor) antibody prophylaxis: a prospective, longitudinal cohort study. *Cephalalgia*. 2022;42(4–5):326-334.
36. Lee MJ, Al-Karagholi MAM, Reuter U. New migraine prophylactic drugs:current evidence and practical suggestions for non-responders to prior therapy. *Cephalalgia*. 2023;43(2):3331024221146315.
37. Rizzi M, Tonello S, Morani F, et al. CGRP plasma levels correlate with the clinical evolution and prognosis of hospitalized acute COVID-19 patients. *Viruses*. 2022;14(10):2123.
38. Ihara K, Ohtani S, Watanabe N, et al. Predicting response to CGRP-monoclonal antibodies in patients with migraine in Japan: a single-centre retrospective observational study. *J Headache Pain*. 2023;24(1):23.
39. García-Castillo MC, Sierra-Mencía Á, Caronna E, et al. Concomitant anti-CGRP and immunomodulatory treatments in patients with migraine: towards integrated management strategies. *J Neurol*. 2025;272(6):443.
40. Ray JC, Cheema S, Foster E, et al. Autonomic symptoms in migraine: results of a prospective longitudinal study. *Front Neurol*. 2022;13:1036798.
41. Waliszewska-Prosół M, Raffaelli B, Straburzyński M, Martelletti P. Understanding the efficacy and tolerability of migraine treatment: a deep dive into CGRP antagonists. *Expert Rev Clin Pharmacol*. 2024;17(11):1039-1051.
42. Cavestro C, Ferrero M. Migraine in systemic autoimmune diseases. *Endocr Metab Immune Disord Drug Targets*. 2018;18(2):124-134.

SUPPORTING INFORMATION

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

How to cite this article: García-Castillo MC, Sierra-Mencía Á, Caronna E, et al. Evaluation of the effectiveness and safety of anti-CGRP monoclonal antibodies in patients with migraine and autoimmune diseases: IMMUNO-CGRP study. *Headache*. 2026;00:1-12. doi:10.1111/head.70086

15264610, 0, Downloaded from https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.70086 by Universidad De Zaragoza, Wiley Online Library on [07/04/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License