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Is achieving higher standards in real-world migraine care feasible with anti-CGRP monoclonal antibodies preventive therapies?: Insights from the EUREkA cohort

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Abstract

Background: The International Headache Society has proposed new treatment goals for migraine prevention in real world, as a way to set higher standards of care. This study provides the first assessment of the proportion of individuals achieving them after 6 months of migraine-specific treatment with anti-CGRP monoclonal antibodies (MAbs).

Methods: This was a prospective, real-world, European multicenter study, including adults with migraine treated with anti-CGRP MAbs (EUREkA cohort). We assessed the proportions of individuals in each treatment goal category–migraine freedom (no monthly migraine days [MMD]); optimal control (< 4 MMD), modest control (4–6 MMD); insufficient control (>6 MMD)–after 6 months of treatment. We also assessed the proportion of individuals with ≥50% reduction in MMD in the insufficient control group.

Results: Of the 5818 individuals in the EUREkA cohort, 4963 had 6 months data. Of these, 82.3% (4086/4963) were females and the median age was 48.0 [40.0–55.0] years. At baseline, the median monthly headache days [MHD] and MMD were 20.0 [13.3–28.0] and 15.0 [10.0–20.0], respectively. All participants were classified as having insufficient headache control (>6 MMD) at baseline. At month 6, 6.9% (342/4963) had migraine freedom, 22.9% (1137/4963) optimal control, 24.6% (1223/4963) modest control and 45.6% (2261/4963) insufficient control. In the insufficient control group, 27.1% (613/2261) had ≥50% reduction in MMD.

Conclusions: High standards of care, defined as optimal disease control or even migraine freedom, are achieved in real-world settings with anti-CGRP MAbs in approximately 30% of individuals with a high migraine burden. These findings highlight the need to expand global access to these treatments. Future studies should explore whether initiating migraine-specific preventive treatments earlier could further reduce residual migraine days in responders, enabling a larger proportion of patients to achieve optimal disease control.

Keywords

migraine, CGRP, monoclonal antibodies, standard of care, optimal control, insufficient control

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Introduction

Migraine-specific treatments, antagonizing the calcitonin-gene related peptide (anti-CGRP) have changed the scenario of migraine prevention. In fact, in real-world studies, 1 in 2 people with migraine when treated with these medications achieves more than 50% reduction in monthly headache days (MHD) with excellent tolerability.[1] The possibility of treating individuals with effective, well-tolerated, disease-specific medications can change the perspective on the standards of migraine prevention we should be aiming for, and set ambitious treatment goals for optimal outcomes in migraine care. A definition of higher standards in migraine care has been proposed by the International Headache Society (IHS) in a recent position statement.[2] Four treatment goal categories have been identified: migraine freedom (no monthly migraine days [MMD] or moderate-to-severe headache days [MSHD]); optimal control (< 4 MMD or MSHD), modest control (4–6 MMD or MSHD); insufficient control (>6 MMD or MSHD).[2] Since the definition is new, it has yet to be assessed if and to what extent migraine-specific drugs, such as anti-CGRP monoclonal antibodies (MAbs), help achieve the new standards of migraine care.

This study aims to provide the first assessment of the proportion of migraine patients achieving the IHS-defined treatment goals after 6 months of treatment with anti-CGRP MAbs using the EUREkA cohort, the largest real-world anti-CGRP cohort to date.

Methods

This is a prospective multicenter real-world study. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline[3] was followed as well as the guidelines of the International Headache Society for Real-World Evidence studies in migraine.[4] Adults with migraine treated with anti-CGRP MAbs (erenumab 70 mg or 140 mg monthly, galcanezumab 120 mg monthly + 240 mg loading dose, fremanezumab 225 mg monthly or fremanezumab 675 mg quarterly) were included. The study cohort and the methodology for data collection have been reported in a previous paper.[1] For this secondary analysis, we used the IHS definitions for treatment goal categories: migraine freedom (0 MMD); optimal control (< 4 MMD), modest control (4–6 MMD); insufficient control (>6 MMD). The primary outcome was the proportion of individuals treated with anti-CGRP MAbs in each category after 6 months of treatment. The secondary outcome was the proportion of subjects with ≥50% reduction in MMD at 6 months in the insufficient control category.

For the statistical analysis, we reported nominal (categorical) variables as frequencies (percentages), whereas the median and

Table 1. Baseline characteristics of the study cohort

Variables	Total (%) (N = 4963)
Demographics	
Country	
Spain	3212 (64.7%)
Italy	1222 (24.6%)
Portugal	221 (4.5%)
UK	122 (2.5%)
Norway	92 (1.9%)
Germany	63 (1.3%)
Poland	31 (0.6%)
Age	48.0 (40.0, 55.0)
Sex (female)	4086 (82.3%)
Reproductive status*	
Active	2191 (44.1%)
Perimenopause/menopause	1895 (38.2%)
Medical history	
Arterial hypertension	571 (11.5%)
Obesity	598 (12.0%)
Cardiovascular disease	229 (4.6%)
Anxiety	1703 (34.3%)
Depression	1464 (29.5%)
Migraine characteristics	
Diagnosis	
Episodic migraine	1417 (28.6%)
Chronic migraine	3546 (71.4%)
Duration of migraine disease, year	29.0 (19.0, 38.0)
Aura	924 (18.6%)
Unilateral pain	2935 (59.1%)
Allodynia	2574 (51.9%)
Nausea/vomiting	3430 (69.1%)
Unilateral cranial autonomic symptoms	1009 (20.3%)
Headache frequency, day/month	20.0 (13.3, 28.0)
Migraine frequency, day/month	15.0 (10.0, 20.0)
Acute medication frequency, day/month	15.0 (10.0, 24.0)
Medication overuse	3125 (63.0%)
Medication history	
Total preventive medication failures	4.0 (3.0, 5.0)
Preventive medication failures	
≤4 failures	3402 (68.5%)
>4 failures	1561 (31.5%)
Previous preventive medication	
Topiramate	4198 (84.6%)
Amitriptyline	4193 (84.5%)
Beta-blockers	3571 (72.0%)
Flunarizine	2996 (60.4%)
Antihypertensive drugs	891 (18.0%)
OnabotulinumtoxinA	3061 (61.7%)
Anti- CGRP MAb treatment	
Erenumab 70 mg	1153 (23.2%)
Erenumab 140 mg	1139 (22.9%)
Galcanezumab 120/240 mg	1398 (28.2%)
Fremanezumab 225 mg (monthly)	1033 (20.8%)
Fremanezumab 675 mg (quarterly)	240 (4.8%)
Concomitant preventive medication	
Oral medication	2420 (48.8%)
Onabotulinumtoxin A	631 (12.7%)
Patient- reported outcomes	
Disability (MIDAS), score	65.0 (36.0, 105.0)
Headache- related impact (HIT- 6), score	67.0 (64.0, 71.0)

†Data from women

Continuous data is represented in median (IQR) and categorical data in % (n). IQR: interquartile range; MIDAS: migraine disability assessment; HIT-6: headache impact test; Antihypertensive drugs (Angiotensin-II receptor blockers, Angiotensin-converting enzyme inhibitors).

interquartile range (IQR) were reported for continuous variables. All analyses were performed using R (version 4.4.2).

Results

Cohort description

Thirty-five European hospitals from 7 countries participated (Spain, Italy, Portugal, United Kingdom, Germany, Norway, Poland).

Of the 5818 individuals of the EUREkA cohort, 4963 had 6 months data: 82.3% (4086/4963) were females and median age was 48.0 [40.0–55.0] years (See Table 1 for other baseline characteristics). Seventy-one-point-four percent (3546/4963) had a baseline diagnosis of chronic migraine. At baseline, the median MHD and MMD were 20.0 [13.3–28.0] and 15.0 [10.0–20.0], respectively. According to the IHS definition, all participants were classified as having insufficient headache control at baseline.

IHS treatment goals after 6 months of treatment

At month 6 of treatment with anti-CGRP MAbs, individuals were classified as: 6.9% (342/4963) migraine freedom, 22.9% (1137/4963) optimal control, 24.6% (1223/4963) modest control and 45.6% (2261/4963) insufficient control (Figure 1).

In the insufficient control group, 27.1% (613/2261) of individuals were ≥50% responders.

Discussion

This is the first study assessing IHS-defined treatment goals in the real world and it is based on the largest cohort of migraine people (EUREkA) treated with anti-CGRP MAbs. We would like to draw attention to two important findings.

First, our migraine population experienced a high disease burden at baseline, with many participants suffering from

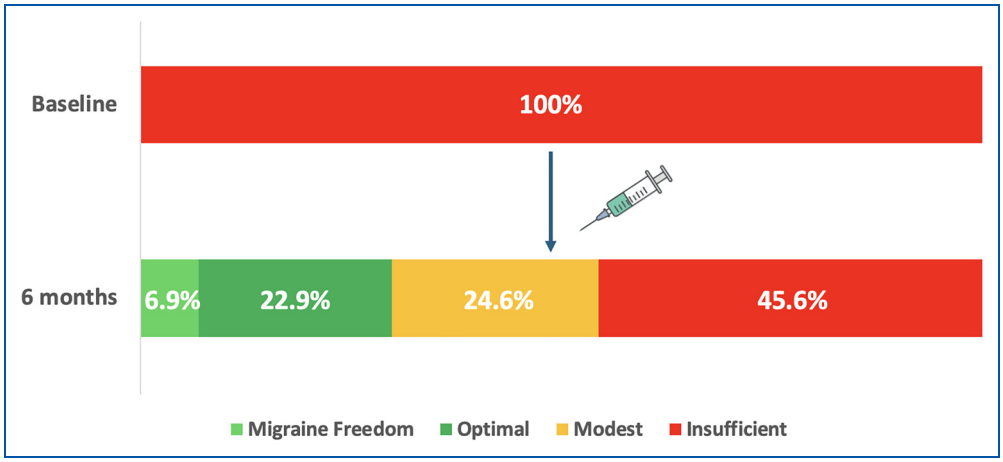

Figure 1. Proportions of people with migraine with insufficient, modest, optimal control and migraine freedom according to the IHS definition at baseline and after 6 months of treatment with anti-CGRP monoclonal antibodies for migraine prevention

chronic migraine, medication overuse, and multiple preventive treatment failures.[1] However, thanks to migraine-specific treatments, approximately 30% achieve optimal disease control (<4 MMD) or even migraine freedom at 6 months. These findings highlight the potential to achieve high standards of care for a significant proportion of highly disabled individuals, underscoring the need to make these treatments more widely and easily accessible on a global scale.[5,6]

Second, the concept of higher standards extends beyond a 50% response to treatment. In our study, approximately one in four participants with insufficiently controlled migraine after six months of monoclonal antibody therapy achieved a ≥ 50% reduction in monthly migraine days. This is because some individuals for whom anti-CGRP treatments are effective, have such a high baseline of MMD that their migraine frequency remains above the threshold for optimal control. It is reasonable to consider whether starting migraine-specific preventive treatments earlier could reduce the number of residual migraine days, thereby allowing a greater proportion of individuals to achieve optimal control. Our previous study[1] demonstrated that initiating anti-CGRP treatment earlier increases the likelihood of a response. Building on this, the current study raises the hypothesis that, among those who respond, earlier intervention could further enhance disease control. However, for some individuals, it is also possible that more time under treatment will be necessary to achieve better responses (later-responders).[7]

Regarding study limitations, those related to multicenter data collection have already been addressed in our previous paper.[1] To mention, cutaneous allodynia was assessed through clinical interview rather than formal testing; however, interviews were conducted by headache specialists, which increases the reliability of the assessment. In this analysis, the main limitation is that the IHS definition was assessed at a single time point (6 months) rather than across the previous three months. However, these definitions are only "ideally" or "if possible" assessed over 3 months.[2] So, while our approach may simplify this aspect on the other it has the strength of gathering the data from a large cohort of participants, providing a preliminary picture of the new treatment goals with anti-CGRP MAbs in the real world.

Conclusion

In this largest anti-CGRP MAbs real-world cohort (EUREkA), 30% of people with a high migraine burden are able to achieve an optimal disease control (fewer than 4 monthly migraine days) or even migraine freedom with anti-CGRP MAbs, demonstrating the potential to reach high standards of care. Future studies should assess if this proportion can be increased by earlier migraine-specific preventive treatment strategies, able to ensure that, for those who respond, the residual migraine burden is reduced.

Article highlights

- Anti-CGRP monoclonal antibodies provide optimal disease control (fewer than 4 monthly migraine days) or even migraine freedom at 6 months in around 30% of patients with high migraine burden in the real world
- Among those with insufficient control, 27.1% still achieved ≥50% reduction in monthly migraine days
- Expanding global access and exploring whether earlier preventive treatment can reduce residual burden in responders may be key strategies to achieving optimal disease control

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Italian Migraine Registry (IGRAINE) study group

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Ethical considerations

The study was approved by the Vall d'Hebron Ethics Committee (EOM(AG)009/2023(6101)) as the coordinating center and shared with all participating centers. All participating centers gave their consent to the use of their data and, if necessary, local ethical approval to pool data was obtained. Data were anonymized and handled confidentially. No informed consent for this study was obtained from patients, considering that they had previously consented to the collection and use of anonymous data at each center, and no additional procedure, data collection or requirement was needed for the current study. The study was conducted in accordance with the declaration of Helsinki.

Patient and public involvement

Neither patients nor the public were involved in the conception or conduct of the study. No dissemination plan has been done.

Transparency statement

The manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as originally planned have been explained.

Consent for publication

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Author contributions

PPR and EC made substantial contributions to conception and study design. All authors worked for acquisition of data. EC and RMDV contributed to data analysis. All authors contributed to the interpretation of data. EC and RMDV wrote the first draft. All authors critically revised and finally approved the version to be published. All authors fully comply with and approve the version to be published.

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