

HERCULES: A REAL-WORLD STUDY ON THE EFFECTIVENESS AND TOLERABILITY OF ANTI-CGRP PROPHYLACTIC TREATMENTS FOR MIGRAINE. PROTOCOL OF THE ONGOING NATIONAL MULTICENTER REGISTRY BY THE HELLENIC HEADACHE SOCIETY

Theodoros S. Constantinidis¹, Evaggelos Kouremenos^{1,2}, Ermioni Giannouli^{1,3}, Nikolaos Fakas^{1,4}, Chryssa Arvaniti^{1,5}, Themistoklis Kalamatas^{1,3}, Efthimios Dardiotis⁶, Spyridon Konitsiotis⁷, and Dimos-Dimitrios Mitsikostas^{1,8}, on behalf of the Hellenic Headache Society

¹ Hellenic Headache Society, Athens, Greece

² 251 Air Forces General Hospital of Athens, Neurology Department, Athens, Greece

³ Department of Neurology, Athens Medical Centre, Marousi, Athens, Greece

⁴ Neurology Department, 401 Army General Hospital of Athens, Athens, Greece

⁵ Neurology Department, Korgialenio-Benakio Greek Red Cross General Hospital of Athens, Athens, Greece

⁶ Department of Neurology, University Hospital of Larissa, School of Health Sciences, Faculty of Medicine, University of Thessaly, Larissa, Greece

⁷ Department of Neurology, University of Ioannina, Ioannina, Greece

⁸ First Neurology Department, Aeginition Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Η μελέτη HERCULES, της Ελληνικής Εταιρείας Κεφαλαλγίας (ΕΕΚ), στοχεύει στην αξιολόγηση της αποτελεσματικότητας και ανεκτικότητας των μονοκλωνικών αντισωμάτων κατά του CGRP στην προφυλακτική θεραπεία της ημικρανίας υπό πραγματικές συνθήκες. **Μέθοδοι:** Πρόκειται για συνεχιζόμενη, προοπτική, εθνική, πολυκεντρική μελέτη καταγραφής που συμμετέχουν δημόσια εξωτερικά ιατρεία κεφαλαλγίας. Συμμετέχουν ασθενείς με επεισοδιακή ημικρανία (8–14 ημέρες/μήνα), που έχουν αποτύχει σε ≥ 3 προφυλακτικές θεραπείες. Τα δεδομένα συλλέγονται μέσω ειδικά ανεπτυγμένου λογισμικού και περιλαμβάνουν ιστορικό, κλινική/παρακλινική εξέταση, ημερολόγιο κεφαλαλγίας και ερωτηματολόγιο (MIDAS, HIT-6, MSQv2.1). Οι επανεκτιμήσεις γίνονται στους 3 μήνες και ανά εξάμηνο για 2 έτη. **Αποτελέσματα:** Αξιολογούνται οι μηνιαίες ημέρες ημικρανίας, ποσοστά ανταπόκρισης $\geq 50\%$, ανεπιθύμητες ενέργειες και ποιότητα ζωής. Αποκλείονται ασθενείς με ενεργή αγγειακή νόσο, κύηση, σοβαρές ψυχιατρικές διαταραχές ή σοβαρή δυσκοιλιότητα (κυρίως για το Erenumab). **Συμπεράσματα:** Η HERCULES παρέχει αξιόπιστα δεδομένα πραγματικής κλινικής πρακτικής για τις αντί-CGRP θεραπείες στην Ελλάδα, συμβάλλοντας στη βελτιστοποίηση των θεραπευτικών αποφάσεων.

Λέξεις-κλειδιά: Ημικρανία, Κεφαλαλγία, Μονοκλωνικά Αντισώματα, Αντί-CGRP, Προφυλακτική αγωγή

HERCULES: ΜΙΑ ΜΕΛΕΤΗ ΠΡΑΓΜΑΤΙΚΟΥ ΚΟΣΜΟΥ ΓΙΑ ΤΗΝ ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ ΚΑΙ ΤΗΝ ΑΝΟΧΗ ΤΩΝ ΑΝΤΙ-CGRP ΠΡΟΦΥΛΑΚΤΙΚΩΝ ΘΕΡΑΠΕΙΩΝ ΚΑΤΑ ΤΗΣ ΗΜΙΚΡΑΝΙΑΣ. ΠΑΡΟΥΣΙΑΣΗ ΤΟΥ ΠΡΩΤΟΚΟΛΛΟΥ ΤΟΥ ΣΥΝΕΧΙΖΟΜΕΝΟΥ ΕΘΝΙΚΟΥ ΠΟΛΥΚΕΝΤΡΙΚΟΥ ΜΗΤΡΩΟΥ ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΕΤΑΙΡΕΙΑΣ ΚΕΦΑΛΑΛΓΙΑΣ

Θεόδωρος Σ. Κωνσταντινίδης¹, Ευάγγελος Κουρεμένος^{1,2}, Ερμιόνη Γιαννούλη^{1,3}, Νικόλαος Φάκας^{1,4}, Χρύσα Αρβανίτη^{1,5}, Θεμιστοκλής Καλαμάτας^{1,3}, Ευθύμιος Δαρδιώτης⁶, Σπυρίδων Κονιτσιώτης⁷ και Δήμος-Δημήτριος Μητσιώστας^{1,8}, εκ μέρους της Ελληνικής Εταιρείας Κεφαλαλγίας.

¹ Ελληνική Εταιρεία Κεφαλαλγίας, Αθήνα

² Νευρολογική Κλινική, 251 ΓΝΑ, Αθήνα

³ Ιατρικό Κέντρο Αθηνών, Αθήνα

⁴ Νευρολογική Κλινική, 401 Γενικό Στρατιωτικό Νοσοκομείο, Αθήνα

⁵ Νευρολογική Κλινική, Γενικό Νοσοκομείο Αθηνών Κοργιαλένιο-Μπενάκειο-ΕΕΣ, Αθήνα

⁶ Νευρολογική Κλινική Πανεπιστημίου Θεσσαλίας, Πανεπιστημιακό Γενικό Νοσοκομείο Λάρισας, Λάρισα

⁷ Νευρολογική Κλινική Πανεπιστημίου Ιωαννίνων, Πανεπιστημιακό Γενικό Νοσοκομείο Ιωαννίνων, Ιωάννινα

⁸ Α' Νευρολογική Κλινική Εθνικού & Καποδιστριακού Πανεπιστημίου Αθηνών, Πανεπιστημιακό Νοσοκομείο «Αιγινήτσιο», Αθήνα

ABSTRACT

Background: The HERCULES study, initiated by the Hellenic Headache Society (HHS), aims to evaluate the real-world effectiveness and tolerability of anti-CGRP monoclonal antibodies for migraine prophylaxis.

Methods: This is an ongoing, prospective, national multicentre registry involving public outpatient headache clinics across Greece. Eligible participants are patients diagnosed with episodic migraine (8–14 migraine days/month) who have failed at least three standard prophylactic therapies. Data are collected using a dedicated digital platform, including headache history, neurological exams, paraclinical tests, headache diaries, and validated questionnaires (MIDAS, HIT-6, MSQv2.1). Follow-up visits are scheduled at 3 months and every 6 months thereafter for 2 years. **Results:** Outcomes assessed include changes in monthly migraine days, $\geq 50\%$ response rates, adverse events, and quality of life. Patients with active vascular disease, pregnancy, major psychiatric conditions, or severe constipation (for Erenumab) are excluded. **Conclusion:** HERCULES provides structured real-world data on anti-CGRP prophylactic therapies for migraine in Greece. The results are expected to inform clinical practice and optimise treatment selection based on effectiveness, tolerability, and patient characteristics.

Keywords: Migraine, Headache, Monoclonal Antibodies, Anti-CGRP mAbs, Prophylaxis.

INTRODUCTION AND OBJECTIVES

The Hellenic Headache Society (HHS) has established a collaborative network of outpatient headache clinics, primarily located in public hospitals (University, National Health System, and Military institutions). This initiative aims to document both primary and secondary headache disorders under real-world conditions (RW).

A list of the participating clinics can be accessed via the following link on the HHS website: <https://kefalalgia.gr/index.php/el/>. Upon accessing the link, users should select “ΙΑΤΡΕΙΑ ΚΕΦΑΛΑΛΓΙΑΣ-ΔΗΜΟΣΙΑ” (Public Headache Clinics) to view the list.

Currently, the primary focus of the ongoing HHS protocol is the documentation of anti-CGRP (Calcitonin Gene-Related Peptide) treatments used as prophylactic pharmacotherapy in migraine patients. The study is conducted in collaboration with BECRO® company (A Contract Research Organisation-CRO) to ensure the implementation of the necessary hardware and software infrastructure required for the consistent recording and monitoring the collection of relevant clinical data across the network.

INFRASTRUCTURE AND TECHNICAL IMPLEMENTATION

A custom software solution was developed using Microsoft Visual Studio 2019 and the ASP.NET v4.7 programming environment. The system is hosted on a Windows Server 2016 platform with IIS 10.

PROTOCOL OVERVIEW

The study protocol, developed in accordance with the guidelines of both the Hellenic Headache Society and the European Headache Federation,^[1,2] includes the following key components:

- Acquisition of informed consent from all participating patients.
- Comprehensive headache history, including identification of trigger factors, associated symptoms, major comorbidities, acute medication use or overuse, and family history.
- Full clinical neurological examination.
- Paraclinical investigations when clinically indicated (e.g., laboratory tests, neuroimaging, EEG).
- Completion of a paper-based or electronic headache diary.
- Administration of validated Greek versions of standardised questionnaires, including MIDAS, HIT-6, and MSQv2.1.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Patients diagnosed with episodic migraine, defined as experiencing between 8 and 14 migraine days per month (d/m) over the preceding 3-month period.
- Documented failure of at least three standard-of-care prophylactic therapies due to lack of efficacy or safety/tolerability concerns, as a prerequisite for social security reimbursement.

Exclusion Criteria

- Patients with active vascular diseases (e.g., stroke, coronary artery disease, uncontrolled arterial hypertension, particularly relevant for Erenumab).
- Pregnant or breastfeeding women.
- Women intending to become pregnant were advised to wait at least six months following discontinuation of anti-CGRP therapy before conception.
- Patients with active major psychiatric disorders (e.g., psychosis).
- Erenumab was avoided in patients with a history of severe constipation and uncontrolled arterial hypertension.

Follow-Up and Outcome Measures

Initial follow-up was scheduled at 3 months post-initiation of therapy, with subsequent evaluations conducted every 6 months for a total duration of 2 years. Outcome measures assessed at each visit included:

- Monthly headache days.
- Proportion of patients achieving a $\geq 50\%$ reduction in monthly migraine days (50% response rate).
- Occurrence of adverse effects.
- Quality of life, as assessed by standardised questionnaires.

FUNDING

The study was supported by unrestricted research grants from the Pharmaceutical companies Teva, Pfizer, Pharmaserve-Lilly, and Lundbeck.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

References

- [1] 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;23:67. <https://doi.org/10.1186/s10194-022-01431-x>
- [2] Mitsikostas DD, Alexoudi A, Arvaniti C, et al. Hellenic Headache Society Recommendations for the Use of Monoclonal Antibodies Targeting the Calcitonin Gene-Related Peptide Pathway for the Prevention of Migraine and Cluster Headache-2023 Update. *SN Compr Clin Med.* 2023;5:118. <https://doi.org/10.1007/s42399-023-01452-w>