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ABSTRACTS

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Title: Antibodies against CGRP do not induce changes in cortical inhibition.

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Background: Monoclonal antibodies against CGRP or its receptor constitute the first migraine-specific prophylaxis therapy. It is not yet clear whether the antibodies have an action on the central nervous system, in addition to the known peripheral action at the neuro-vascular interface.
A way to verify the level of cortical excitability is through the recording the cortical silent period (CSP). CSP is induced delivering transcranial magnetic stimulation (TMS) pulses over the motor cortex and by recording the electromyographic (EMG) activity from the contracted perioral muscles. CSP is defined as the interruption of voluntary EMG activity that follows a single TMS. The aim of our study was to evaluate whether monoclonal antibody against CGRP treatment has a central effect on cortical motor inhibitory circuits, assessed by studying the CSP.

Methods: We prospectively enrolled 8 migraine patients from those attending our Headache Center, 4 with episodic high-frequency migraine (9 -14 days/month) and 4 with chronic migraine (≥ 15 days/month for at least 3 months). In all patients, during the pain-free phase, we recorded CSP from the perioral muscles, by TMS, at baseline (T0), 30 days (T1), and 60 days (T2) before each injection of galcanezumab or fremanezumab.

Results: The mean number of days with headache/month was significantly reduced, from T0 to T1 ($p = 0.017$) and from T0 to T2 ($p = 0.003$). The duration of CSP did not change significantly from T0 to T1 ($p = 0.405$) and from T0 to T2 ($p = 0.953$). We did not find a significant correlation between the percentage change in CSP and the change in headache days ($p = 0.570$).

Conclusions: From our preliminary data, treatment with monoclonal antibody against CGRP showed no central cortical effects on GABAergic inhibitory circuits, neither early after 1 month nor late after 2 months of treatment.

Title: Successful treatment of chronic migraine comordids with myasthenia gravis and arthritis with nonoclonal antibody against CGRP: a case report.

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Introduction: Monoclonal antibodies against CGRP and its receptor are the first target therapy for migraine prevention. CGRP is a 37-aminoacid peptide produced in central and peripheral sensory neurons throughout the CNS. This peptide is also localized in nonneuronal tissues throughout the body. For this reason, some researchers emphasized that circulating antibodies could affect all peripherally accessible sites where CGRP acts. CGRP-immunoreactive fibers were identified in the thymus, where it inhibits IL-2 production and proliferation of thymocytes in vitro. Transcription of the acetylcholine receptor alpha subunit, the main autoantigen in myasthenia gravis (MG), is induced by CGRP and VIP in human thymus and thymomas from MG patients. Autoimmune dysfunction of CGRP and its receptors is postulated to give rise to fatigue-related conditions such as chronic fatigue syndrome. Nonetheless, CGRP plays a role in the painful component of other chronic pain conditions, such as arthritis.

Case report: A 49 year old woman presented to our clinic in 2016 with a history of chronic migraine. She had twenty days of headache per months. She has had 2 episodes of visual aura. Her neurologic examination was negative. She tried 3 oral preventive therapies: with amitriptyline she had no efficacy, with calcium channel blocker and topiramate she had no durable improvement. In 2019 she presented chronic fatigue and blurred vision, performed EMG repetitive stimulation, and Myastenia gravis was diagnosed without specific antibodies, for this reason she began pyridostigmine bromide therapy. In 2021, for her chronic joint pain, she was diagnosed with psoriatic arthritis and fibromyalgia, for this reason she started therapy with methotrexate and folate once a week. Meanwhile her headache became daily and disabling, so she started therapy with fremanezumab 225 mg once a month with important improvement of her migraine: after 3 months she had only 2 migraine attacks per months with less intensity and duration.

Discussion and conclusions: As mentioned above, a CGRP-related mechanism has been hypothesised for myasthenia, chronic fatigue, and arthritis, all pathologies comorbid with chronic migraine in our patient. In this case report, anti-CGRP molecule fremanezumab did not interfere negatively with the other comorbid conditions.

Title: Expression of miR-155 in migraine: association with different phenotypes and disease severity.

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Background: At present, there are no validated and reliable biomarkers of migraine, but the headache scientific community is intensely investigating the molecular signatures of migraine. microRNAs are small endogenous noncoding RNAs that operate as post-transcriptional regulators of gene expression. Several recent lines of preclinical evidence highlighted the role of miR-155 in inflammation and pain generation and maintenance. In the present study we aim to study the role of miR-155 in migraine, with a particular interest in its association with migraine phenotype and disease severity.

Methods: This is a cross-sectional and controlled study involving three study groups: healthy controls (HCs), episodic migraine (EM) and chronic migraine with medication overuse headache (CM-MOH). We assessed the expression of miR-155 (Relative Quantification - RQ) in peripheral blood monocytes. All determinations were performed in the inter-ictal migraine phase.

Results: Demographic features were comparable among the three study groups. Anxiety was more represented in CM-MOH when compared to EM (p=0.046). miR-155 expression was analysed in 23 HCs (0.5±0.16 RQ), 52 EM (1.73±2.09 RQ), and 31 CM-MOH (2.65±2.39 RQ) subjects. Migraine patients showed higher miR-155 expression when compared to HCs (p=0.001). In addition, miR-155 expression was higher in CM-MOH patients when compared to EM group (p=0.002). This finding was confirmed in a logistic regression (EM vs CM-MOH; p = 0.019), after controlling for age, sex, ongoing preventive treatment, and psychological comorbidities.

Conclusion: Our findings suggest that miR-155 is elevated in migraine patients, and associated with disease phenotype. The study of microRNAs may represent a useful tool to characterize different phenotypes across the migraine spectrum. In addition, microRNAs may represent novel molecular targets for drug development (“antagomir”).

Title: Unmet needs and challenges in the management of drug-resistant migraine non-responsive to CGRP(R) monoclonal antibodies

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Background: The introduction of anti-calcitonin gene related peptide (CGRP) or its receptor (CGRP-R) monoclonal antibodies (mAbs) has significantly changed the treatment of migraine, providing target-specific, effective and well tolerated drugs. However, about 25-30% of patients did not achieve a clinical meaningful response (assessed with different migraine-related variables), leading to treatment discontinuation with few other treatment options. Herein, we evaluate the follow-up of non-responder-patients (NR) that discontinued anti-CGRP(R) mAbs.

Methods: We performed a retrospective analysis including all outpatients with chronic (CM) or high frequency episodic migraine (HFEM) treated which one anti-CGRP(R) mAbs that discontinued treatment for ineffectiveness only. NR patients were defined as patients achieving <50% response rate in monthly headache days (MHDs; according to pivotal clinical trials) and a <50% MIDAS score reduction (according to the Italian Medicines Agency [*AIFA*] reimbursement criteria) at three and six months of treatment or any moment thereafter. After discontinuation, patients‘ status and the introduction of new treatments were reported. The choice of the new preventive treatment was clinically-based on previous failures, patients’ preference, and migraine severity.

Results: Between December 2019 and February 2023, n=495 patients with CM or HFEM were treated with anti-CGRP(R) mAbs and 180 (36.5%) discontinued treatment for any reason. Among these latter, 110 (61.1%) had a complete follow up and discontinued due to ineffectiveness (n=102, 92.7%), adverse events (n=4, 3.6%), or other reasons (n=4, 3.6%). After discontinuation of anti-CGRP(R) mAbs for only ineffectiveness, 57 (55.8%) of NR patients started a new preventive treatment, 37 (36.2%) were lost to follow up and 8 (7.8%) decided to not start a new preventive treatment. Among patients who started a new treatment, 44 (77.1%) patients switched anti-CGRP mAb (ligand to receptor or *viceversa*), 5 (8.7%) patients started OnabotulinumtoxinA, and 8 patients started and oral treatment (14.0%) with one or more drugs among olanzapine, lamotrigine, candesartan, topiramate or amitriptyline.

Conclusion: The treatment of patients who are non-responsive to anti-CGRP treatment remains a challenge and requires tailored management strategies that take into consideration their clinical profiles, preferences, and needs.

Title: "Dim Light Melatonin Onset" and chronotype profiling in patients with episodic and chronic migraine

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Background: Chronic migraine with medication overuse headache (CM-MOH) represents one of the most disabling phenotypes across the migraine spectrum. Patients with CM-MOH suffer several comorbidities, including sleep disorders. The aim of this study is to better define the chronotype of migraine patients by means of subjective clinical scales and salivatory melatonin measurements.

Methods: We enrolled 40 patients with CM-MOH, 18 patients with episodic migraine (EM) and 32 healthy controls (HCs). All subjects completed the Morningness–Eveningness Questionnaire (MEQ), the Pittsburgh Sleep Quality Index (PSQI) and a prospective sleep diary, and underwent 5 saliva melatonin samplings (at hourly intervals with the first sample collected 3 h before the subject's regular bedtime). We calculated the "Dim Light Melatonin Onset" (DLMO), a well-known biological marker of circadian phase in humans. Furthermore, we considered the clinical and demographic features and the psychological profile of subjects enrolled.

Results: EM patients were younger when compared to CM-MOH patients and HCs. According to the PSQI, symptoms of depression and anxiety and sleep disturbances were more frequent in CM-MOH when compared to EM, as expected. MEQ score was higher in CM-MOH (59.6±7.7) when compared to EM (53.3±11.9, p=0.045) and HCs (51.0±10.1, p=0.001). According to MED, a subjective morningness profile was more prevalent in CM-MOH (56.8%) when compared to EM (33.3%) and HCs (17.2%) (p=0.001). DLMO occurred earlier in CM-MOH (20:31±52 minutes) and in EM (20:28±0:49 minutes) when compared to HCs (21:17±63 minutes; p=0.05 and p=0.014, respectively). This was confirmed in a multinominal regression after correction for age and sex. DLMO did not differ between CM-MOH and EM groups (p=1.000). According to DLMO, a biological morningness profile was more prevalent in CM-MOH (32.4%) and in EM (33.3%) when compared to HCs (7.4%) (p=0.019).

Conclusion: Migraine patients showed a morning-oriented chronotype when compared to HCs. Chronotype evaluated according to DLMO did not differ between CM-MOH and EM, suggesting an endogenous phenotype of migraine biology without association with

disease severity. By contrast, CM-MOH patients described themselves as more morning oriented, showing a role of behavioral aspects related to the more severe phenotype of disease.

Title: Do novel European Headache Federation criteria identify differences in migraine burden? Baseline data of an international real-life study on resistant and refractory migraine (REFINE).

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Background. In 2020, the European Headache Federation (EHF) performed an expert consensus to provide a definition of resistant and refractory migraine. We aimed at testing these criteria and evaluating patients' evolution over time.
Methods. We performed a longitudinal, multi centre, international study (REFINE study). Through this ad interim analysis, we aimed at evaluating EHF criteria discriminate patients with different levels of migraine-related burden at enrolment. Therefore, we compared baseline characteristics, comorbidities, and patients reported outcomes (PROMs) of non-resistant and non-refractory, resistant and refractory migraine patients enrolled.

Results. We included 574 patients from 15 European headache centres: 317 (55.2%) with non-resistant and non-refractory, 215 (37.5%) with resistant and 42 (7.3%) with refractory migraine.

Patients with resistant and refractory migraine, as compared to those with non-resistant and non-refractory, reported more often a diagnosis of tension type headache (84.1%, 95.0%

vs. 58.8%; p≤0.001), chronic migraine (68.8%, 71.4% vs. 37.9%%; p≤0.001) with longer history of chronification (median months [IQR] = 40.0 [15.0-96.0], 60.0 [24.0-114.0] vs. 24.0 [12.0-60.0]; p≤0.001), and medication overuse (49.8%, 50.0% vs. 20.5%; p≤0.001).

Resistant and refractory migraine patients also had more comorbidities compared to non-resistant and non-refractory migraine patients, such as depression (33.2%, 42.9% vs. 16.3%; p≤0.001), anxiety (23.8%, 34.1% vs. 13.3%; p≤0.001), and sleep disturbance (41.1%, 43.9% vs. 29.8%; p=0.013). PROMs also revealed a higher presence of anxiety (p≤0.001) and depression (p≤0.001) symptoms, and poorer sleep quality (p≤0.001) in resistant and refractory migraine patients. Regarding specific perceptions about migraine, resistant and refractory individuals reported higher impact of migraine on daily life (p≤0.001) and work, household work, and social life (p≤0.001) when compared to non-resistant and non-refractory subjects.

Conclusion. Resistant and refractory migraine are associated with relevant migraine burden considering migraine features, comorbidities and scores at several scales; therefore, these ad interim analysis showed that EHF diagnostic criteria for resistant and refractory migraine effectively resemble patients' burden.

Title: Headache in the elderly: a single centre small study. Preliminary study on headache in elderly

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Background. Although headache is a common cause of disability especially among young women, it is also a common source of complaint among people older than 50 years. We conducted a single centre observational study in which we collected demographic data, headache characteristics and comorbid medical conditions (psychiatric and cognitive). We also considered diagnosis of Medication- Overuse Headache (According to the international classification of the Headache disorders III).

Methods. Among 450 patients (≥ 16 years old) evaluated between January and June 2019 for the first time in our secondary headache centre or at the emergency department of our hospital, 75 aged ≥50 were recruited. Patients older than 50 with secondary headache were excluded.

Results. Mean age was 60.3 years. 45 (60%) were diagnosed with migraine and 13.33% of them presented aura (all of them declared visual symptoms). 25 patients with migraine declared >15 episodes/months treated with Non Steroidal Antinflammatory Drugs (NSAIDS) greater than or equal to 15 days per month. 16 patients (64%) declared had never been evaluated before in headache centre. 6 patients (24%) had been previously evaluated by psychiatrists due to mood disorders. Other 8 patients (32%) admitted cognitive or mood disorders not evaluated before (2 patients were referred to memory centre due to low Mini- Mental State Evaluation score <24/30, 4 were treated with antidepressants drugs (Geriatric Depression Scale >10 score).

Conclusion. Proper treatment of headache in older people requires recognition of comorbidities and drug induced or medication overuse headache. General practitioners should refer patients, even if older than 50, to a headache centre, especially when attacks are recurrent and a suspected cognitive or psychiatric comorbidity has been suspected. If a primary headache has been suspected also neurologists should consider to manage patients with other specialists such as psychiatrists or geriatricians.

Title: Do chronic patients with a short migraine history respond better to monoclonal antibodies targeting the CGRP?

Authors: Federico De Santis, Chiara Rosignoli, Valeria Caponnetto, Agnese Onofri, Davide Ciuffini, Susanna Ratti, Valentina Taranta, Eleonora De Matteis, Raffaele Ornello and Simona Sacco.

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Background: Monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) are a potential first-line treatment for patient with migraine who are severely disabled by the disease, like chronic patients whose progressive, worsening condition leads to a long burdensome disease. We aim to evaluate whether the years of chronic migraine history influence the outcomes of treatment with mAbs.

Methods: We analyzed data from patients with chronic migraine treated with mAbs in our center. We calculated the response rate to the drug as percent change in Monthly Migraine Days (MMD) from the third month of treatment to baseline, then we divided patients in two groups according to the MMD response rate: non responders (up to -50% reduction), responders (more than -50% reduction). We tested the correlation between the percent response rate and patients' age and overall years of migraine history. We used the Pearson correlation test, Spearman Rho correlation test and the Mann Whitney's U test.

Results: Overall, 139 patients (87.1% females; median age 49.5, Interquartile Range (IQR) 40.75-57.25 years, median migraine onset 18.0, IQR 13.0-27.25 years, median mAb's starting age47.0, IQR 37-55 years) were included. One hundred and fifteen (82.7%) had a diagnosis of chronic migraine. Among them we found a linear inverse correlation between percent MMD response rate and years of migraine history before the mAb (p=0.023) and mAb starting age (p=0.004, Spearman's ρ=0.295).
Responders, compared with non-responders, had a lower median age (46.5, IQR 41-53, vs 59, IQR 50-67; p=0.001), lower median age at migraine chronification (33.5 years, IQR 27.25-41.75, vs 40 years, IQR 28-50; p=0.014); a lower median mAb's starting age (43, IQR 37-50, vs 55.5, IQR 48-64.25, p<0,001) and a lower median number of disease history years (24, IQR 17-30, vs 30, IQR 18.75-46.25, p= p=0.026).

Conclusion: According to our results, patients with a shorter history of chronic migraine were more likely to respond to mAbs compared with those with a longer disease history. It is crucial to intercept the chronicity of the disorder as early as possible in order to deploy effective treatments to change the course of migraine.

Title: Acetaldehyde via CGRP receptor and TRPA1 in Schwann cells mediates ethanol-evoked periorbital mechanical allodynia in mice: relevance for migraine

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Background: Ingestion of alcoholic beverages is a known trigger of migraine attacks. However, whether and how ethanol exerts its pro-migraine action remains poorly known. Ethanol stimulates the transient receptor potential vanilloid 1 (TRPV1) channel, and its dehydrogenized metabolite, acetaldehyde, is a known TRP ankyrin 1 (TRPA1) agonist.

Methods: Periorbital mechanical allodynia following systemic ethanol and acetaldehyde was investigated in mice after TRPA1 and TRPV1 pharmacological antagonism and global genetic deletion. Mice with selective silencing of the receptor activated modifying protein 1 (RAMP1), a component of the calcitonin gene-related peptide (CGRP) receptor, in Schwann cells or TRPA1 in dorsal root ganglion (DRG) neurons or Schwann cells, were used after systemic ethanol and acetaldehyde.

Results: We show in mice that intragastric ethanol administration evokes a sustained periorbital mechanical allodynia that is attenuated by systemic or local alcohol dehydrogenase inhibition, and TRPA1, but not TRPV1, global deletion, thus indicating the implication of acetaldehyde. Systemic (intraperitoneal) acetaldehyde administration also evokes periorbital mechanical allodynia. Importantly, periorbital mechanical allodynia by both ethanol and acetaldehyde is abrogated by pretreatment with the CGRP receptor antagonist, olcegepant, and a selective silencing of RAMP1 in Schwann cells. Periorbital mechanical allodynia by ethanol and acetaldehyde is also attenuated by cyclic AMP, protein kinase A, and nitric oxide inhibition and pretreatment with an antioxidant. Moreover, selective genetic silencing of TRPA1 in Schwann cells or DRG neurons attenuated periorbital mechanical allodynia by ethanol or acetaldehyde.

Conclusion: Results suggest that, in mice, periorbital mechanical allodynia, a response that mimics cutaneous allodynia reported during migraine attacks, is elicited by ethanol via the systemic production of acetaldehyde that, by releasing CGRP, engages the CGRP receptor in Schwann cells. The ensuing cascade of intracellular events results in a Schwann cell TRPA1- dependent oxidative stress generation that eventually targets neuronal TRPA1 to signal allodynia from the periorbital area.

Title: Predictors of early efficacy of monoclonal antibodies therapy in migraine: investigating the central role of GCRP through structural equation modelling

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Background: Migraine represents nowadays one of the leading causes of disability and loss of working days in the world. Innovative therapies targeting the CGRP signaling opened and established a new era in preventive treatment of migraine. Post marketing efficacy evidences are convincing and the neurobiological context of CGRP modulation is a field of growing interest though its relationship with clinical results is still scarcely investigated.

Methods: we enrolled 41 patients (34 F, 7 M; age 52.16 ± 12.47 years; 24 CM, 17 EM) who started mAbs therapy (7 Erenumab, 17 Galcanezumab and 17 Fremanezumab). During the first visit (T0) they underwent plasmatic CGRP, Orexin-A (OxA) and PACAP-38 measurement and collection of clinical-anamnestic information. The clinical course was re-evaluated at 3 months (T3), based on monthly migraine days (MMD), monthly medication use, mean pain intensity (NRS) and MIDAS. Data were analyzed by S.E.M. (Structural Equation Modeling) to develop a predictive model of treatment response based on T0 clinical and biochemical characteristics. This multivariate analysis defines new composite variables (called latent variables) through quantitative relationships with the observed variables. Thus, we obtained the latent variables NeuP, i.e. "Neuropeptides" (CGRP, PACAP-38 and Orexin-A) and MigBurd T0 i.e. "Migraine burden" (MIDAS and MMD at T0). Then, via S.E.M., we correlated them with T3 clinical outcome.

Results: CGRP plasmatic concentration at T0 emerged as a unique independent predictor of therapeutic response at T3 through direct correlation with MMD (100 pg/ml per 1,7 MMD at T3; $p = 0.032$). Through S.E.M. we found a similar correlation also with monthly medication use and MIDAS at T3. The latent variable MigBurd T0 was directly correlated with all three above mentioned parameters, while baseline CGRP prevailed over NeuP latent variable as predictor of MMD and MIDAS at T3.

Conclusion: The neurobiological setting may be crucial in the variability of clinical response to mAbs therapy even in the short term (first trimester) period. Though further data are needed to generalize these results, the present study confirm our previous findings about the predictive role of baseline GCRP plasmatic concentration in the context of preventive anti-CGRP therapy.

Title: Does the number of previous failures predict the response to monoclonal antibodies acting on the CGRP pathway?

Authors: Rosignoli C., Ornello R., Caponnetto V., Onofri A., De Santis F., De Matteis E. and Sacco S.

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Background: Monoclonal antibodies acting on the calcitonin gene-related peptide pathway (CGRP mAbs) are the first drugs developed for migraine preventive treatment and are effective for patients resistant to other treatments[1,2].
This study aims to assess whether the number of failures to preventive treatments predicts 3-month response to -CGRP mAbs.

Methods: We followed-up to 3 months patients with migraine who started treatment with Anti-CGRP mAbs (erenumab, fremanezumab or galcanezumab). At baseline visit, we collected sociodemographic data, medical history, and number of failures in preventive treatment due to ineffectiveness or intolerance.
We compared the numbers of failures in prior preventive treatments in 50% responders – i.e., those reporting a ≥50% decrease in monthly migraine days from baseline – vs non-50%-responders.

Results: We included 139 patients (87.1% women, 82.7% with chronic migraine) treated with Anti-CGRP mAbs (39.6% erenumab 70mg, 21.6% erenumab 140mg, 14.4% galcanezumab, 23.7% fremanezumab). We found 31 (22.3%) >50% responders 101 (72.7%) patients had <4 and 37 (36.6%) ≥ 4 failures.
At baseline – i.e., during the 3 months before treatment start –, median monthly migraine days (MMD) was 17.5 (IQR 12-30], at 3 months MMD decrease to 7 (IQR 3-15.50, p<001). We found no correlation between the total number of prior failures and the response rate to the anti-CGRP mAbs (>50% $\boldsymbol{\rho}_s$:0.028 p=0.762; $\boldsymbol{\rho}_s$:-0.061 ≥75% p=0.506, Spearman's correlation). The median number of failures for the entire group was 3 [interquartile range (IQR) 2-4). For >50% responders, the median number of failures was 3 (IQR 2-3), while for ≥75% responders was 3 (IQR 2-4), however, this difference was not significant (p=0.886).

Conclusion: This study showed a significant reduction in MMD after 3 months of treatment with anti-CGRP mAbs. However, we did not find an association between the number of failures to preventive treatment and the response rate to anti-CGRP mAbs, suggesting that response to monoclonal antibodies is independent of the prior treatment failures.

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Title: Effectiveness and tolerability of rimegepant as acute treatment in a patient with refractory migraine and non-responder of two anti-CGRP monoclonal antibodies and oral triptans: a case report

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Background: Small molecule receptor antagonists (gepants), or monoclonal antibodies (mAbs) against calcitonin gene related peptide (CGRP), have recently become available for migraine prophylaxis with proven efficacy. If the failure to an anti-CGRP(R) mAbs preclude the effectiveness of gepants or viceversa is still unknown. Herein, we report the case of a patient with refractory migraine responsive to the acute use of rimegepant 75 mg that previously failed two different anti-CGRP(R) mAbs and with no response to other acute treatments including triptans.

Methods: The patient was instructed to collect effectiveness and tolerability of rimegepant 75mg for every attack of moderate to severe intensity, after 2 hours from administration on an electronic diary. The variables collected include: rating of headache severity, absence or presence of migraine-associated symptoms, use of rescue medications, the rating of functional disability and recurrence of headache pain at different time points. After 24h the patient collected the eventual re-occurrence of migraine, the use of rescue medication and migraine-related symptoms and disability. The effectiveness was definite as 2h pain freedom. Sustained pain freedom after 24h was also considered.

Results: A 56-year-old female patient with a long history of migraine without aura and chronic migraine. She reported having daily headaches that were severe in intensity. She reported no effect from the use of oral triptans or other oral symptomatic drugs. The patient reported failure for ineffectiveness or not tolerability of all classes of preventive pharmacological treatments (fulfilling refractory criteria) included galcanezumab (240 mg loading dose than 120 mg monthly) and erenumab (70 mg then 140 mg). The patient has completed the e-dairy for 5 attacks with intake of rimegepant 75 mg with an achievement of 2h pain free on 3/5 attacks with sustained response after 24 h and no rescue medication used. In the remaining 2 attacks the patients reported no changes and the need of rescue medications. The drug was taken at the onset of the headache attack (range 10-30 minutes) for all attacks. No adverse events were reported. The patient reported a better efficacy of the drug compared to previous intakes of triptans.

Conclusion: Rimegepant 75 mg used as acute treatment seems to be effective and well tolerated in a patient with prior failures to two anti-CGRP(R) mAbs and no response to oral triptans. To the best of our knowledge, this is the first case of a patient assessing the use of rimegepant 75 mg as acute treatment in a patient with refractory migraine who failed two anti-CGRP mAbs.

Title: Use of anti-CGRP monoclonal antibodies in pediatric migraine: first evaluations of a phase 3, randomized, double-blind, placebo-controlled study.

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Background: to date, prophylactic therapies for migraine include the use of antiepileptic drugs, calcium antagonists or antidepressants. In recent years, studies have been conducted on adults with the monoclonal antibody that binds the receptor of the peptide related to the calcitonin gene (CGRP), which competes specifically with the binding of CGRP to its receptor by inhibiting its function. CGRP modulates the nociceptive signal and is associated with the pathophysiology of migraine. Therapies currently available in children have limited efficacy. There is therefore a need for additional drugs.

Methods: 8 patients with chronic migraine and 3 patients with episodic migraine were enrolled in the study according to the criteria of the International Classification of Headaches (ICHD-III). Patients with chronic migraine are in the following phases: 4 finished the study, 1 dropped out, 1 in the double-blind phase, 2 in the open-label and dose-blind phase. Patients with episodic migraine are all in doble-blind phase.

Results: among the 8 patients with chronic migraine, it can be stated that 4 patients reported a reduction in the frequency and intensity of monthly migraine attacks and 1 patient reported the ineffective therapy: while two patients in the open-label and dose-blind phase and one patient in the double-blind phase are still under evaluation. In three of the four patients with chronic migraine, who had a good response to therapy, a reduction in the frequency and intensity of monthly attacks was observed starting from the double-blind phase. All 3 patients with episodic migraine are still under evaluation.

Conclusion: to date our preliminary data on the efficacy of anti-CGRP antibodies in pediatric age, even if under evaluation, confirm what has been found in double-blind studies on the adult population, or the possibility of having a prophylactic drug specific and efficacy for migraine. However, more pediatric studies will be needed to confirm these preliminary results.

Title: A real-life study over three one-year cycles of treatment with CGRP-targeting monoclonal antibodies in a cohort of chronic migraine patients

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Background: In Italy, antibodies targeting CGRP pathway (mAbs) are subsidized for 1-year cycles separated by a mandatory interruption of at least 1 month. Few data is available regarding mAbs effectiveness after the 1-year treatment cycles and the mandatory suspension periods. Our aim was to evaluate mAbs effectiveness across 3 consecutive 1-year cycles (namely C1, C2 and C3) and related suspension periods.

Methods: We evaluated 38 patients with chronic migraine and medication overuse headache (CM+MOH) (68.4% females, 51.8±10.3 years). All patients were responders to mAbs and completed three 1-year cycles (T_0 to $T1_{12}$ for C1, S1 to $T2_{12}$ for C2, and S2 to $T3_{12}$ for C3) with erenumab or galcanezumab. Each cycle was separated by a suspension period of at least 3 months (S1 and S2). Co-primary outcomes were changes in monthly migraine days (MMDs) from baseline (calculated in the 3 months prior to each cycle) i) during each cycles, and ii) during the suspension periods. As secondary outcome we considered changes in migraine-related disability (assessed using MIDAS questionnaire) at the same timepoints.

Results: MMDs showed an early and stable improvement in all of the three consecutive cycles (C1: T_0 22.6±5.0 vs. $T1_{12}$ 7.9± 3.5, p<0.0001, C2: S1 18.3±5.9 vs. $T2_{12}$ 8.4±4.1, p<0.0001; C3: S2 14.4±5.5 vs. $T3_{12}$: 8.1±4.1, p=0.003). MMDs worsened during the suspension periods (S1 vs. $T1_{12}$ p<0.0001; S2 vs. $T2_{12}$ p<0.0001). Notably, during S1 MMDs reached the pretreatment baseline (T_0), while during S2 they remained lower compared to T_0 value (p<0.0001). MIDAS scores behaved accordingly (C1: T_0 68.7±55.7 vs. $T1_{12}$ 16.3± 20.6, p<0.0001, C2: S1 59.1±35.6 vs. $T2_{12}$ 23.4±27.1, p<0.0001; C3: S2 39.5±25.7 vs. $T3_{12}$: 17.8±14.1, p=0.006).

Conclusion: In our population of CM-MOH, mAbs induced an early and sustained reduction in MMDs during three one-year cycles of treatment. MMDs significantly worsened during suspension periods, although they did not reach the pretreatment level starting from the second suspension, namely after two years of mAbs treatment. The zenith of improvement was comparable at the end of all cycles, suggesting a *floor effect*.

Title: "Plantar Reflexology as a Complementary Therapy for Headache Management: A Scoping Review"

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Background: Headaches are a common ailment that affects individuals of all ages and genders. While pharmaceutical interventions for headache management are available, some individuals seek alternative therapies such as reflexology.
This critical review of literature aims to examine the effectiveness of plantar reflexology as a potential therapy for headache management.

Methods: A systematic search of databases was conducted, and published studies were analyzed for their quality and efficacy of plantar reflexology in headache management.

Results: From 23 initial registrations, 2 studies fulfilled the inclusion criteria. One article was an RTC and a pilot sudy. The studies showed a significant increase in treatment efficacy compared to the control group. However, more high-quality studies are needed to confirm these findings and elucidate the underlying mechanisms of plantar reflexology in headache management.

Conclusion: This review highlights the potential of plantar reflexology as a complementary therapy for headache management. Further research is needed to confirm these findings and better understand the mechanisms behind the efficacy of plantar reflexology in headache management. Overall, plantar reflexology shows promise as a safe and non-invasive alternative therapy for those seeking natural approaches to headache management.

Title: Refractory Chronic Cluster Headache successfully treated with Galcanezumab 240 mg: a case report

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Background: Calcitonin gene-related peptide monoclonal antibodies (CGRP-mAbs) are a promising preventive therapy for cluster headache (CH), but their efficacy, particularly in chronic CH (cCH), is not yet well established. In randomized controlled trials, galcanezumab was successful in treating episodic CH (eCH) but failed in cCH. Here we present a case of a refractory cCH patient successfully treated with galcanezumab.

Methods: The patient is a 34-year-old woman with a history of chronic migraine. In the last 3 years, she developed cCH ab initio, with a stable frequency of 3-6 attacks per day with typical left side-locked headache associated to ipsilateral autonomic signs and symptoms. Each attack lasted no more than 2 hours and had excellent response to sumatriptan. She failed several preventive agents, including 5 antiepileptics, verapamil, indomethacin, steroids, melatonin and greater occipital nerve blocks. Ketogenic diet was the most effective treatment, although without a long-lasting benefit. Her ongoing prophylaxis was prednisone 50 mg daily, without significant benefit. Given her complex clinical history, she was started on off-label galcanezumab 240 mg monthly, and her response was monitored over the next weeks.

Results: The patient experienced a dramatic response to galcanezumab, with complete remission of CH attacks in the weeks following treatment initiation. Steroids were discontinued, and the patient remained headache-free on 240 mg of galcanezumab monthly for two months before being titrated down to 120 mg. Dose titration resulted in headache recurrence. Reinstating the 240 mg dose led to complete remission, and the patient is currently on stable treatment with no other CH medications.

Conclusion: This case report suggests that galcanezumab may be a viable preventive therapy at least in a subset of cCH patients. The patient's history of chronic migraine may suggest a more CGRP-dependent phenotype, which may have contributed to the success of treatment. Further studies are warranted to investigate the role of CGRP-mAbs in cCH and to identify patient subgroups that may benefit most from this therapy. This case highlights the importance of exploring alternative treatments for refractory CH patients and providing access to CGRP-directed therapies in this difficult cohort of patients.