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ABSTRACTS

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Differences between migraineurs responders and non-responders to monoclonal antibodies acting on the CGRP pathway: a subgroup analysis of baseline data from an international real-life study on Resistant and rEFractory migraINE (REFINE)

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Background: The description of characteristics of non-responders to monoclonal antibodies acting on the CGRP pathway (anti-CGRP moAbs) would contribute to the scientific debate on the topic and orient future research.

Methods: We considered baseline data form an international real-life study on Resistant and rEFractory migraINE (REFINE). We compared responder patients (i.e., continued the prescribed treatment) with non-responders to anti-CGRP moAbs (i.e., the therapy was described as 'not effective') regarding sociodemographic and anamnestic characteristics, headache diagnosis, history and current pattern, and questionnaires.

Results: Among 139 patients with available information on anti-CGRP moAb response, non-responders were 56 (40.3%), while responders were 83 (59.7%). Compared with responders, non-responders reported higher median number of months of migraine chronification (median = 36, IQR = 11-84 vs. median = 0, IQR = 0-48; p = 0.001), total headache days (median = 8, IQR = 0-15 vs. median = 5, IQR = 0-10; p = 0.025), monthly migraine days (median = 15, IQR = 10-20 vs. median = 10, IQR = 6-15; $p \leq 0.001$), number of failed preventatives (median = 6, IQR = 5-7 vs. median = 4, IQR = 4-6; $p \leq 0.001$), monthly days of symptomatic drugs assumption (median = 16, IQR = 8-20 vs. median = 10, IQR = 7-15; p = 0.003, Headache Impact Test-6 score (median = 66, IQR = 61-68 vs. median = 61, IQR = 57-66; p = 0.001), Headache Attributed Lost Time score (median = 51, IQR = 23-118 vs. median = 23, IQR = 13-39; $p \leq 0.001$), Hospital Anxiety and Depression Scale – depression symptoms score (median = 8, IQR = 5-11 vs. median = 6, IQR = 2-9; p = 0.019), Insomnia Severity Index score (median = 13, IQR = 4-19 vs. median = 7, IQR = 4-15; p = 0.030).
Compared with responders, non-responders reported significantly higher percentages of tobacco smoking (14.3% vs. 6.0%, p = 0.027), ongoing antidepressant therapy (50.0% vs. 26.5%, p = 0.005), ongoing anxiolytic therapy (30.4% vs. 14.5%, p = 0.024), and chronic migraine (80.4% vs. 43.4%, $p \leq 0.001$), while responders reported significantly higher percentages of caffeine consuming (90.4% vs. 71.4%, p = 0.004) and thyroiditis (20.5% vs. 3.6%, p = 0.004) compared with non-responders.

Conclusion: Non-responders to anti-CGRP moAbs reported clinical characteristics of worse migraine pattern and longer preventative history compared to responders, together with different life habits and higher migraine impact on life, mood, and sleep.

Serum CGRP as a marker for migraine: a critical appraisal of methodologies and findings

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Background: To this point, there are no reliable, migraine-specific biomarker in the objective diagnosis of migraine. Recent studies suggested that the trigeminovascular peptide calcitonin gene-related peptide (CGRP) is a possible mediator of migraine and hence a potential biomarker. The pivotal role of CGRP in migraine is substantiated by the development of targeted treatments targeting the CGRP peptide or its receptor. The aim of this study was to summarise the current evidence assessing serum CGRP as a diagnostic biomarker of migraine.

Methods: A comprehensive literature search was conducted on PubMed for related publications from inception to April 1, 2022. The process of identification, selection and critical appraisement of the studies followed the PRISMA criteria for systematic reviews.

Results: We included 12 studies. Most studies used ELISA assays (n = 11, 92%), one study used a radioimmunoassay method. Considering the ELISA findings, serum CGRP levels appear very heterogeneous and difficult to replicate in healthy volunteers (range: 2.02-26900 pg/ml), interictal episodic migraine patients (range: 6.38-220.40 pg/ml) and interictal chronic migraine patients (range: 6.24-393.30 pg/ml). At a graphical inspection, CGRP does not discriminate between the three populations. Only one study has been conducted in ictal migraine patients.

Conclusion: Serum CGRP measured in healthy volunteers, interictal episodic and chronic migraine patients is highly heterogeneous, possibly due to a poor reproducibility among ELISA assays. Five different commercial ELISA kits were used, while three studies did not report the name of the commercial kit. Whether the negative results are due to methodological issues or CGRP being an unsuitable biomarker for migraine remains unclear.

Periorbital nociception in a progressive multiple sclerosis mouse model is dependent on TRPA1 channel activation

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Background: The transient receptor potential ankyrin 1 (TRPA1) is involved in acute and chronic pain generation, and its activation is mediated by several exogenous and endogenous agonists such as hydrogen peroxide (H2O2) and 4-hydroxynonenal (4-HNE) that are increased in mouse and rat models of periorbital and facial nociception, such as migraine-like behaviour. Moreover, TRPA1 activation leads to calcitonin gene-related peptide (CGRP) release, an endogenous compound related to headache development. Headache can be present in several pathologies, including progressive multiple sclerosis (PMS), Thus, our main purpose was to optimise the development of PMA in a PMS-EAE model and detect the role of TRPA1 in this nociceptive behavior.

Methods: To induce a mouse model of PMS-EAE, the mice were immunised with an emulsion of MOG35-55 administered by a subcutaneous (s.c.) route in the flank region. Subsequently, all animals received a dose of 300 ng of pertussis toxin, which was re-administered 48 h after the induction.
Periorbital mechanical allodynia (PMA) was assessed on days 3, 5, 7, 9, 11, 13, and 14 after PMS-EAE induction. Sumatriptan, olcegepant, TRPA1 selective antagonists A967079 and HC-030031, non-selective antagonists metamizole and propyphenazone, or TRPA1 knockout mice and the anti-oxidants α-lipoic acid and apocynin were used to evaluate the PMA.

Results: PMS-EAE-induced mice showed a reduction in periorbital mechanical threshold from day 7 to 14 post-induction. TRPA1 genetic deletion (Trpa1-/- mice) provided an inhibition on the development of PMA, moreover the systemic administration of sumatriptan, olcegepant, TRPA1 antagonists A967079, HC-030031 metamizole and propyphenazone were able to reduce PMA after until 2 hours after administration. The PMS-EAE induction was able to increase oxidative markers in the trigeminal ganglion, increasing levels of 4-HNE, H2O2 and NADPH oxidase. And treatment with the antioxidants α-lipoic acid and apocynin was able to decrease PME.

Conclusion: TRPA1 channel seems a valuable therapeutic target for PMS-EAE-induced nociception, such as neuropathic pain and PMA. These results suggest that the generation of TRPA1 endogenous agonists in the PMS-EAE mouse model may sensitise TRPA1 in trigeminal nociceptors to elicit PMA, since the treatment with antioxidants was able to decrease PMA.

Neuropeptides modulation during monoclonal antibodies therapy in migraine: a pilot study investigating the role of CGRP, Orexin-A and PACAP

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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 a new era in preventive treatment of migraine. In particular, anti-CGRP (Fremanezumab and Galcanezumab) and anti-CGRP receptor (Erenumab) monoclonal antibodies (mAbs) represented the first validated and specific migraine prevention. Post marketing efficacy data are accumulating worldwide but, at the same time, the neurobiological context of CGRP modulation and its relationship with clinical results was scarcely investigated.

Methods: This is a pilot study of CGRP, Orexin-A (OrxA) and PACAP plasmatic variations in relation with clinical outcome during "anti-CGRP" therapy. We enrolled fifty-five consecutive migraine patients (episodic or chronic) who were eligible to mAbs preventive treatment based on AIFA reimbursement criteria. Sixteen of them underwent plasmatic CGRP, OrxA and PACAP dosing at the time start of the treatment and after six months. A group of sixteen age and sex matched non migraineur volunteers was enrolled, the same blood sampling procedure was performed in this group. A comprehensive set of clinical and demographic data was collected at baseline and at three and six months follow-up in migraine patients.

Results: Treatment efficacy on both pain and functional outcome was confirmed: NRS, MIDAS, mean monthly migraine days (MMD) and migraine attack treatment use were significantly reduced after 6 months ($p<0.001$). OrxA emerged as an inverse independent predictor of clinical response (NRS, MIDAS, MMD and medication use; $p<0.05$ in multivariate analysis). Basal CGRP level inversely correlated with 6 months clinical outcome ($p<0.001$ in correlation with MMD, MIDAS and medication number reductions). Concerning comparison with control group, OrxA and PACAP levels were significantly higher in patients at baseline ($p<0.05$ and $p< 0.001$ respectively).

Conclusions: Though further studies are needed, this work deepens insights into neuropeptides modulation during anti-CGRP therapy in migraine patients. In particular, here we suggest a possible association between OrxA and clinical outcomes even in the context of CGRP signaling inhibition while the role of baseline CGRP as a predictor of efficacy needs to be further investigated.

Efficacy of erenumab treatment on allodynia: real-world data

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Background: Allodynia is a frequently occurring symptom in migraine patients who report pain even from slight tactile stimuli. Allodynia is interpreted as a sign of central sensitization to pain and is typical of chronic migraine. Monoclonal antibodies acting on the CGRP pathways have peripheral targets, while allodynia is viewed as a central phenomenon. Therefore, it would be interesting to assess whether monoclonal antibodies, which desensitize the periphery, can also have a central de-sensitization effect indicated by decreased allodynia. The aim of this study was to verify the trend of allodynia and pain-related disability in patients treated with erenumab at baseline (T0, i.e. the three months preceding the treatment) and after three months of treatment (T1).

Methods: Patients with chronic migraine (CM) (ICHD-3 criteria) were consecutively recruited in the years 2020-2021 at the Headache Center of Avezzano-L'Aquila. Erenumab was prescribed according to clinical practice criteria. At both T0 and T1, patients filled out the Allodynia Symptom Checklist (ASC-12) for assessment of allodynia and MIDAS and HIT-6 tests for assessment of migraine pain-related disability. Monthly migraine days at T0 and T1 were assessed by a headache diary.

Results: We included 28 patients with CM (93% women) median age of 50 years (IQR 40-55). At T1, compared with T0, patients reported a significant decrease in median monthly migraine days (7, IQR 5-13; vs 20, IQR 12-25; $p<0.001$), of median monthly days of use of over-the-counter analgesics (5, IQR 0-11; vs 9, IQR 2-18; $p=0.027$) and of triptans (0, IQR 0-4; vs 0, IQR 0-13; $p=0.016$). The ASC-12 median score decreased from 7 (IQR 5-9) to 4 (IQR 3-7) $p=0.009$. We also observed statistically significant differences in MIDAS (T0=50, IQR 28-81; T1=12, IQR 0-33; $p=0.001$) and HIT-6 (T0=67, IQR 63-69; T1=62, IQR 54-65; $p=0.002$) scores.

Conclusion: Although limited by the absence of neurophysiological demonstration, our data suggest that erenumab treatment is associated not only with improvements in migraine frequency, disability, and acute medication use, but also in allodynia, which indicates a potential central de-sensitizing effect of the drug.

Prevalence of migraine in patients with endometriosis and its association with pelvic pain

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Background: Endometriosis and migraine are two disabling disorders with many similarities in terms of clinical manifestations, epidemiology, and pathogenesis. Pain is the main symptom shared by both conditions. Some molecular mechanisms were proposed to explain the association of endometriosis and migraine. Recently, evidence has emerged regarding a correlation between clinical severity and phenotypes of endometriosis and migraine presence. Our objective was to investigate the prevalence of headache and migraine in patients with endometriosis, and to compare characteristics of patients with and without migraine.

Methods: We conducted a retrospective study on 131 women with a diagnosis of endometriosis who were screened for headache between September 2019 and March 2022 at the Careggi Endometriosis clinic. Patients' characteristics, gynaecological history and symptoms related to endometriosis (e.g. dysmenorrhea, dyspareunia, dysuria) were compared between women with or without migraine. Pelvic pain scores and associated symptoms were assessed using a visual analog scale (VAS). Women completed a self-administrated headache questionnaire to assess the occurrence and the type of headache, with specific questions about their characteristics according to the International Criteria of Headache Disorders (ICHD-3).

Results: The prevalence of migraine in women with endometriosis was 53.4% (70/131). Patients with and without migraine had similar age and body mass index. Dysmenorrhea and dysuria were significantly more frequent in patients with endometriosis and migraine as compared to those without migraine ($p=0.03$ and $p<0.01$). No difference was found for other variables such as age at diagnosis and duration of endometriosis, comorbidities, heavy menstrual bleeding, or adenomyosis.

Conclusions: Since over half of the patients with endometriosis suffer from migraine, diagnostic tools for this disorder should be applied sooner in women with endometriosis. Further studies are needed to investigate possible common mechanisms leading to pelvic pain and migraine.

Optimization of acute treatment in migraine patients treated with monoclonal antibodies acting on the CGRP Pathway

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Background: Optimizing acute treatment is essential in the management of migraine. One of the aims of migraine preventive treatments is to improve response to acute migraine treatments. However, it is unknown whether monoclonal antibodies targeting the CGRP pathway (CGRP-MoAbs) can improve response to acute treatments. We evaluated the effect of CGRP-MoAbs on the perceived efficacy of acute treatment using the Migraine Treatment Optimization Questionnaire (mTOQ), a validated, self-administered instrument developed to assess response to acute treatment in people with migraine, where higher scores indicating better effectiveness of acute treatments.

Methods: Patients with chronic and episodic migraine from the Headache Centers of Avezzano-L'Aquila and Naples, were included from March 2021 to April 2022. We included and followed up to 3 months patients starting treatment with CGRP-MoABs (erenumab, fremanezumab, or galcanezumab) at the baseline visit. All patients filled out the mTOQ at both visits. In addition, during the study period, they completed a headache diary, where they reported the number of migraine days and acute drug intakes.

Results: We included 31 patients, (90.3% woman; 67.7% with chronic migraine), median age 46 years [interquartile range (IQR) 42.5–54.5]. At baseline – i.e., during the 3 months before treatment start –, median mTOQ score was 5.5 (IQR 3-8), with 27 median monthly migraine days (IQR 23-50) and a median drugs intake equal to 25 doses (IQR 15-52). At the 3-month follow-up, median mTOQ scores increased to 9.5 (IQR 7-13; $p<0.001$ *vs*. baseline), while median monthly migraine days decreased to 20 (IQR 8-25; $p=0.008$ *vs.* baseline). The median number of acute treatment use decreased from 25 to 20 doses (IQR 8-28 $p=0.01$ *vs* baseline), during the 3 months of follow-up. Finally, higher scores on the mTOQ did not correlate with lower use of acute treatments ($p=0.607$, Pearson's correlation).

Conclusion: Our study shows that, 3 months of preventive treatment with CGRP-MoAbs led to a significant increase in mTOQ scores, meaning improved effectiveness of acute treatments, paralleled by decreased monthly migraine days and acute treatment use.

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Transient receptor potential ankyrin 1 (TRPA1) contributes to mechanical hypersensitivity in a mouse model of endometriosis

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Background: Endometriosis is caused by the presence of endometrial-like tissue outside the uterus and affects ~10% of reproductive-aged women. Patients may present with a variety of symptoms, including abdominal pain or migraine. Preclinical evidence supports the role of oxidative stress in the pathogenesis of endometriosis and related pain symptoms. The transient receptor potential ankyrin 1 (TRPA1) has been identified as a major sensor of oxidative stress, thus contributing to inflammatory, neuropathic, cancer and migraine pain. Here, we hypothesize that TRPA1 plays a critical role in pain symptoms associated with endometriosis.

Methods: To induce endometriosis-like lesions without surgery, dissected uterus horns of donor female mice, previously treated with a subcutaneous injection of estradiol benzoate to stimulate the endometrium growth, were injected intraperitoneally (i.p.) in recipient female mice.
Abdominal mechanical allodynia (AMA), hind paw mechanical allodynia (HMA) and periorbital mechanical allodynia (PMA) was assessed from day 7 to day 28 after endometrium injection. A TRPA1 selective antagonist, A967079, TRPV1, TRPV4 or TRPA1 knockout mice and the free-radical spin trap, N-tert-butyl-alpha-phenylnitrone (PBN) were used. A967079 and PBN were administered to mice at day 28 after endometrial tissue injection.

Results: Endometrial tissue injection caused a time-dependent increase in the number of visible endometrial-like lesions in the abdominal cavity in C57BL/6J female mice. The increase in endometrial-like lesions was paralleled by a time-dependent increase in AMA, HMA and PMA. TRPA1 genetic deletion (*Trpa1*$^{-/-}$ mice) provided full protection against AMA, PMA and HMA compared to wild type (*Trpa1*$^{+/+}$*)* mice. Deletion of TRPV1 and TRPV4 (*Trpv1*$^{-/-}$, *Trpv4*$^{-/-}$ *mice)* did not affect the development of AMA, PMA and HMA compared to wild type (*Trpv1*$^{+/+}$, *Trpv4*$^{+/+}$*)* mice. Systemic (i.p.) treatment at day 28 with A967079 or PBN transiently and completely reversed the AMA, PMA and HMA.

Conclusion: Oxidative stress plays a major role in AMA, HMA and PMA in a mouse model of endometriosis. The reduction in AMA, HMA and PMA after genetic deletion and pharmacological blockade of TRPA1 indicates that the channel is critically implicated in such allodynia. Thus, TRPA1 seems to have a critical role in sensing oxidative stress to sustain mechanical hypersensitivity in endometriosis.