

DECODING THE BIOCHEMICAL SIGNATURE OF TREATMENT-RESISTANT MIGRAINE: SEARCHING FOR DISEASE PHENOTYPES AND NOVEL THERAPEUTIC TARGETS

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Background. Nearly 40% of migraine subjects fail to respond to monoclonal antibodies targeting the calcitonin gene related (CGRP) pathway (mAbs). We hypothesized that these subjects may bear a non-CGRP-dependent phenotype. Alterations in the endocannabinoid system (eCBome), reflected by changes in fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), have been previously demonstrated in migraine (1). The primary aim of the SPHERA project is to assess changes in gene expression of the eCBome catabolizing enzymes in migraine subjects who do not respond to mAbs treatment.

Methods. In this longitudinal prospective study, we enrolled 105 subjects (82.9% women, age 42.1±13.3 years), 55.2% with high frequency episodic migraine, and 44.8% with chronic migraine. We treated 40% of subjects with fremanezumab, 33.3% with galcanezumab, and 26.7% with erenumab. Participants were evaluated at baseline (T0) and after a 3-month mAbs treatment (T1). Subjects not achieving a reduction of at least 50% of monthly migraine days (MMDs) at T1 were classified as Non-Responders. At T0, we performed an extensive biochemical profiling including: gene expression of FAAH and MAGL and other metabolic enzymes of the eCBome system (DAGL, NAPE, NAAA) and microRNAs in peripheral blood mononuclear cells; plasma levels of eCBome associated lipids (PEA, AEA, 2-AG, OEA), neuropeptides (CGRP, PACAP, VIP), pro- and anti-inflammatory cytokines (IL-12, IL-10, TNF-alfa, IFN-γ, IL-2, IL-6), and kinurenic and quinolinic acids.

Results. At T1, 54 subjects (51.4%) classified as Responders. At T0, FAAH expression was higher in Responders (1.713±2.268 RQ) compared to Non-Responders (0.796±0.599 RQ; p=0.009). MAGL expression did not differ between the two groups (Responder: 9.615±6.294 vs. Non Responder: 8.156±5.556; p=0,310). No differences were observed in the remaining biochemical analyses between the two groups.

Conclusions. Non-responders showed reduced FAAH gene expression, consistent with previous evidence. This results in decreased endocannabinoid degradation and consequently higher compensatory eCBome levels aimed at maintaining an antinociceptive effect. Future Non Responders to mAbs treatment display reduced expression of FAAH. This may contribute to a non-CGRP-dependent migraine phenotype with selective eCBome involvement.