PACAP pathway: a new frontier in migraine prevention

Preventive therapies targeting calcitonin gene-related peptide (CGRP)—ie, monoclonal anti-CGRP or anti-CGRP receptor antibodies, which are injected subcutaneously or intravenously, and gepants, which are given orally—have substantially improved therapeutic options and provided relief for many people with migraine. These new therapies offer superior efficacy compared with traditional migraine treatments, as shown in a systematic review and network meta-analysis.[1] However, not all patients respond to therapies targeting the CGRP pathway and alternative biological targets are still under investigation. One such target is pituitary adenylate cyclase-activating polypeptide (PACAP), a neuropeptide implicated in migraine pathophysiology through its roles in vasodilation and nociception. The potential for inhibition of the PACAP pathway to be a novel therapeutic target has been shown in a phase 2 randomised, placebo-controlled trial reported by Messoud Ashina and colleagues,[2] which evaluated the efficacy of Lu AG09222, a humanised monoclonal antibody against PACAP, in patients with episodic or chronic migraine who had not responded to two to four previous preventive treatments.

Participants were randomly assigned in a 2:1:2 ratio to receive a single intravenous infusion of 750 mg Lu AG09222, 100 mg Lu AG09222, or placebo. Compared with the placebo group, the 750 mg group had a statistically significant reduction in migraine days per month after a baseline observation period of 1 month (mean reduction 6·2 days *vs* 4·2 days in the placebo group; difference of 2·0 migraine days [95% CI −3·8 to −0·3]). This reduction is particularly notable given the resistant nature of the participants' migraines, indicating that PACAP inhibition is a promising approach, warranting further research in phase 3 trials.

The implications of this study are substantial because PACAP inhibition has distinct mechanisms of action compared with CGRP-targeted therapies. PACAP is expressed widely in the brain and in other parts of the body and has been implicated in a wide range of physiological functions.[3] PACAP has various roles in the CNS, including regulating circadian rhythms, facilitating learning and memory, modulating anxiety, and contributing to responses to stress and brain injury.[3] In the periphery, PACAP participates in the control of immunity and inflammation, the release of catecholamines from the adrenal medulla, and insulin secretion,[4] and it is a transmitter in autonomic and sensory neurons.[5] Moreover, PACAP concentrations in plasma vary according to the hormonal status of women with migraine.[6]

Its putative role in several physiological systems suggests that PACAP could provide broader therapeutic benefits than those possible with CGRP inhibition, especially for patients with complex migraine symptoms and associated conditions. Migraine is characterised not only by headache but also by prodromal, aura, and non-pain symptoms, such as nausea, photophobia, and cognitive changes.[7] There is a strong influence of sexual hormones as well as comorbidity with cardiovascular and mental health conditions on migraine.[8] Addressing this multifaceted disorder might require combination therapies targeting multiple pathways.

Despite the encouraging results in this phase 2 trial, further research must address long-term safety and efficacy. Phase 3 studies should provide insight into whether the observed reductions in the number of migraine days per month can be sustained. Safety data from the phase 2 trial indicated a favourable tolerability profile during the 12-week observation period, with mild adverse events reported more frequently in the Lu AG09222 750 mg group than in the placebo group, such as COVID-19 (7% *vs* 3%), nasopharyngitis (7% *vs* 4%), and fatigue (5% *vs* 1%). As larger, phase 3 trials are conducted, understanding how PACAP-targeted therapies interact with immune responses and other physiological systems—such as the endocrine system, in which PACAP signalling also has a role—will be crucial for long-term clinical application.

Another important question is whether PACAP-targeted treatments could benefit patients who have a partial response to inhibition of CGRP or its receptors or other preventive therapies (eg, those who have only a 50% reduction in days with a headache, rather than a higher percentage decrease). This phase 2 trial shows efficacy in patients who had not responded to two to four preventive therapies, potentially including anti-CGRP therapies, suggesting that anti-PACAP therapies might fill a crucial therapeutic gap.[9] Further studies will be essential to evaluate the potential for combining

PACAP-targeted therapies with CGRP inhibitors or other treatment approaches, with the aim of providing a comprehensive approach to migraine management.

MFPP has received honoraria for speaking engagements and consulting from Eurofarma, Ache, Libbs, Teva, Abbvie, Pfizer, Lundbeck, Lilly, and Viatris; participates on data safety monitoring boards or advisory boards for Abbvie, Pfizer, Lundbeck, and Teva; has patents planned, issued, or pending for US 17/196,611 and BR202017023353; and has roles in Abraces and the Brazilian Headache Society

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