

NOVEL PHARMACOLOGICAL APPROACHES IN MIGRAINE THERAPY

A. Leo, D. Scuteri

Department of Health Sciences, Magna Graecia University of Catanzaro, Catanzaro, Italy

E-mail: damiana.scuteri@unicz.it**Doi:** 10.36118/pharmadvances.2024.57

On September 19th and 20th, 2024, the University of Calabria, Rende (Cosenza) was venue of the congress "*Novel Pharmacological Approaches in Migraine Therapy*". The latter represented a collaborative scientific initiative of the University of Calabria (Cosenza), University Magna Graecia (Catanzaro), and Sant'Anna Institute (Crotone) under the Auspices of NEXT GENERATION EU (NGEU), the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project Mnesys (PE0000006), the Italian Society of Pharmacology (SIF), the Italian Society of Neuroscience (SINS), the Italian Society for the Study of Headache (SISC), the Italian Society of Neurological Rehabilitation (SIRN), and the Italian Society of Child and Adolescent Neuropsychiatry (SINPIA). The meeting was organized by Professors Antonio Leo and Damiana Scuteri and chaired by Professors Giacinto Bagetta, Maria Tiziana Corasaniti and Giovambattista De Sarro.

Migraine represents one of the most disabling forms of primary headache, with a severe social impact, rank as one of the leading causes of years lived with disability worldwide and therefore considered a very serious public health problem.

Migraine constitutes a substantial public health problem that mainly affects young and middle-aged adults. As widely reported, migraine is often associated to various comorbidities, including epilepsy, attention-deficit hyperactivity disorder, behavioral problems, obesity, atopic dermatitis, asthma, restless legs syndrome, and anemia that negatively impact the quality of life of patients, increasing further the use of health care and medication. Professor Paolo Martelletti (Rome) pointed at the need for training of young physicians in the clinical practice of migraine management. Particularly, Dr Angelo Pascarella (Catanzaro) described how migraine and epilepsy share several clinical features and have intertwined genetic and molecular underpinnings, which may contribute to common pathogenesis.

According to the International Classification of Headache Disorders (third edition) compiled by the International Headache Society, Professor Coppola (Salerno) reported that headache disorders are divided into primary and secondary headaches. Primary headaches represent idiopathic pain conditions such as migraine, tension-type headaches, and trigeminal autonomic cephalalgia (TAC). Secondary headaches result from a severe underlying disorder and are associated with high morbidity and mortality. This group includes conditions such as headaches attributed to a head injury, vascular disorder or infection or psychiatric disorder. In this field, Dr Belardo (Naples) underlined the effect of treatment with pentadecyl-2-oxazoline (PEA-OXA), a natural α -2 antagonist and histamine H3 partial agonist, on systemic pro-inflammatory state, allodynia, and affective disorders associated with social isolation. The most frequent types of primary headaches in the young population are migraine and tension-type headaches. In the context of these patholo-

gies, understanding endogenous and exogenous triggering factors aids the definition of different pathophysiological paradigms for the exercise of research.

Professor Philip Holland (London) explained that knowledge of the pathophysiology of migraine is crucial for identifying new therapies and discussed the importance of neurogenic inflammation and diffuse cortical spreading depression inducing activation of trigeminal neurons. Professor Gary Lawrence (Dublin) underlined the mechanism of action on SNARE gene products of botulinum neurotoxins to modulate CGRP release of identified nerve terminals in several forms of pain including neurogenic inflammation of migraine.

Professor Rossella Nappi (Pavia) described that sex steroids may influence the prevalence of migraine in both sexes. Female sex steroids may modulate different mediators and receptor systems in the pathogenesis of migraine through both genomic and non-genomic mechanisms at peripheral and neurovascular levels. Regarding the pathogenesis of migraine, Professor Stefania Ceruti (Milan) explained that activated glial cells and the linked neuroinflammation worsen the clinical scenario, leading to chronic migraine. Indeed, trigeminal glial cells are involved in the initiation and maintenance of pain in migraine leading to central sensitization. Professor Pierangelo Geppetti (Florence) also discussed the key role of transient receptor potential (TRP) channels in the context of migraine and the program to identify and develop innovative treatments targeting these channels.

Overall, this amount of data underscores the idea that basic research is fundamental both for identifying the pathophysiological features of migraine and to develop innovative therapies.

In the past, this clinical field has been characterized by lack of knowledge of the pathophysiology of the disease, leading to preventive approaches borrowed from drugs originally developed for other therapeutic indications, resulting in limited efficacy and in an unacceptable level of side effects causing poor adherence. Moreover, patients with ascertained primary headache disorders like migraine or tension-type headaches overuse drugs for their acute headaches, inadvertently amplifying the frequency and intensity of their headaches and their refractoriness. Consequently, a vicious cycle of further drug consumption and increased headache frequency develops, converting the treatment for their headache to the cause of the disease. Regarding this aspect, Professor Simona Sacco (L'Aquila) affirmed that medication-overuse headache (MOH) is a common neurologic disorder with an enormous disability that plays an important role in the transformation from episodic to chronic headache disorders.

More than 35 years of pharmacological research have established a sound, rational basis on which the currently available disease-modifying drugs have been developed.

Today, new pharmacological, non-pharmacological, and nutraceutical approaches are being used. Professor Dimos-Dimitrios Mitsikostas (Athens) clarified many pharmacodynamic aspects of the Lasmiditan that acts as selective agonist of the 5-HT_{1F} receptor, representing a promising mechanism-based approach for the treatment of migraine attacks and gained importance over the past few years.

Since 2018, two classes of drugs that counteract the actions of calcitonin gene-related peptide (CGRP), which plays a key role in migraine onset, became available: gepants (CGRP receptor antagonists) and monoclonal antibodies (mAbs) directed against CGRP or its receptor.

It is widely recognized that these drugs represent one of the most significant therapeutic achievements in the treatment of migraine. Due to their protein nature and high molecular weight, it has been proposed that they exert preventive effects by acting directly on the peripheral segment of the trigeminal-vascular system. Indeed, as Professor Marina De Tommaso (Bari) pointed out, thanks to their long half-lives, these molecules revolutionized the prophylactic treatment of this neurovascular disorder. Furthermore, as stated by Professor Alberto Chiarugi (Florence), these

drugs, by preventing chronic pain, remove not only migraine attacks but also all related symptoms, counteracting the awareness of discomfort. In particular, anti-CGRP antibodies seem to significantly impact brain functions of migraineurs, preventing not only migraine headache but also co-existing central, psychiatric symptoms and malaise.

Doctor Damiana Scuteri (Catanzaro) illustrated how the history of CGRP in migraine paves the route to success for key signaling pathways in the modulation of nociceptive facilitation. In particular, the real-world data presented about refractoriness, efficacy and safety point to the need for a clinical trial assessing efficacy and safety of onabotulinumtoxin A in combination with the newest anti-CGRP/R monoclonal antibodies and atogepant, as small molecule CGRP receptor antagonist, for the prevention of chronic migraine.

In this new scenario, however, several pathophysiological, therapeutic, and regulatory issues remain open. As far as the latter topic is concerned, it is crucial to establish new appropriate pharmacovigilance patterns to detect adverse events of anti-CGRP monoclonals in the post-marketing experience, as stated by Doctor Francesca Bosco (Catanzaro).

Professor Stephen D. Silberstein (Philadelphia), introduced the endocannabinoid system and its potential involvement in the pathogenesis of migraine, suggesting cannabinoid-based therapy as an intriguing alternative for the treatment of migraine. According to Doctor Vincenzo Rania (Catanzaro) diamagnetotherapy, a non-pharmacological approach to manage migraine, could represent a non-invasive therapeutic method based on the repulsion mechanisms generated by the forces of high-intensity magnetic fields that can trigger cellular readjustment towards a positive physiological response, improving the quality of life of patients.

Professor Patrizia Popoli projected the picture of the efficacy and reliability of these drugs by addressing some of the uncertainties related to their use in clinical practice, such as their differential efficacy in migraine subtypes, predictors of outcome, switching from one molecule to another, adherence and persistence to long-term treatment, the persistence of effect after discontinuation, combined treatment with botulinum toxin or gepants, cost-effectiveness, and potential contraindications based on the known physiological effects of CGRP.

Furthermore, it is essential to establish serious and reliable networks for the treatment of headaches.

In this context, Professor Domenico Conforti (Rende, Cosenza) illustrated the ALCMEONE industrial research and development project, which aims at providing an innovative organizational and management model and an advanced technology platform of services to support the integrated clinical management of headache patients. The objectives of this project concern the integration of patient-centered healthcare pathways, fully supported by a service platform, assisting the patient in the self-recording of the disease and enabling the primary care level to manage most cases effectively and efficiently. Dr Rita Scarpelli (Catanzaro) carried out evaluations on the cost/benefit ratio of new treatments, illustrating the current data on prescriptions in the Calabria region.

In conclusion, this event involved academic researchers, pharmacologists, clinicians, and national and international leaders who provided postgraduate students, young researchers, and clinicians with their most up-to-date views.

