Proposal of combination therapies to treat refractory chronic migraine

Damiana Scuteri[1,2], Martina Pagliaro[1,2], Andrea Monteleone[1], Assunta Tarsitano[3], Rosario Iannacchero[4], Marilù Vulnera[3], Giorgio Sandrini[5], Paolo Tonin[2], Giacinto Bagetta[1*], and Maria Tiziana Corasaniti[6*]*

[1]Pharmacotechnology Documentation and Transfer Unit, Preclinical and Translational Pharmacology, Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy; [2]Regional Center for Serious Brain Injuries, S. Anna Institute, Crotone, Italy; [3]Provincial Health Authority (ASP), Cosenza, Italy; [4]Department Neurology Headache Center, Hospital Regional "Pugliese-Ciaccio", Catanzaro, Italy; [5]Department of Brain and Behavioral Sciences, University of Pavia, IRCCS C. Mondino Foundation Neurologic Institute, Pavia, Italy; [6]Department of Health Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy. *These Authors share co-first authorship.

Abstract. Chronic migraine, affecting people for over 15 days per month of which 8 show migraine features, severely reduces patients' quality of life with great rate of associated disability. Onabotulinumtoxin A has been used in the prevention of chronic migraine for the last two decades. A recent pooled analysis of real-world data highlighted the efficacy of its use in combination with the most novel monoclonal antibodies targeting the machinery of the calcitonin gene-related peptide (CGRP) in refractory migraine. Moreover, the CRD42023393250 systematic review and meta-analysis registered in the National Institute for Health Research International prospective register of systematic reviews PROSPERO following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement supported the safety of onabotulinumtoxin A, demonstrating that it induces fewer treatment-related adverse events (TRAEs) than oral topiramate one of the most commonly used preventative drugs. Therefore, the present data together with the lack of appropriately designed, prospective studies prompt the proposal of clinical trials to assess the efficacy and safety of the combination treatment of onabotulinumtoxinA with monoclonal antibodies or gepants directed towards the pathway of CGRP.

Key words: chronic migraine, onabotulinumtoxin A, anti-CGRP monoclonal antibodies, atogepant

Resistant migraine and the calcitonin gene-related peptide (CGRP) machinery

Chronic pain from diverse aetiology affects some 30–50% people worldwide: among chronic pain conditions, according to the International Classification of Headache Disorders (ICHD, third revision) beta diagnostic criteria, chronic migraine is characterized as at least 15 headache days per month, of which 8 days present the features of migraine, for three months consecutively (1) and it represents one of the main causes of years lived with disability (2), impairing daily activities in working age mainly. Despite the positive impact of novel specific treatments beyond triptans on the disease (3), a high percentage of patients still does not find relief and effectiveness in current therapies; among other mechanisms, genetic predisposition has been involved (4, 5). Indeed, the discovery of the role of the calcitonin-gene related peptide (CGRP) as a fundamental player of vasodilation and neurogenic inflammation, pivotal in migraine pathophysiology, fostered the development of several novel drugs, abortive and preventative, targeting its machinery (6). The small molecules, known as gepants, and the monoclonal

antibodies (mAbs) aiming at inhibiting the signaling of CGRP are the first Disease-Modifying Migraine Drugs (DMMDs) (7). Gepants are very useful and easy to administer as abortive treatments, due to their oral and intranasal administration route (8, 9). On the preventative side, mAbs directed towards CGRP, i.e. fremanezumab, galcanezumab and eptinezumab, the only administered intravenously with potential for use in acute treatment (10-12), or its receptor complex, i.e. erenumab, were developed and approved for the prevention of episodic and chronic migraine (13).

Onabotulinumtoxin a and novel combination approaches

Botulinum neurotoxin type A is effective in several pain conditions (14, 15), being able to tackle the process of exocytosis of neurotransmitters or neuropeptides, e.g. CGRP (16), by cleaving the 25 kDa synaptosomal-associated protein (SNAP-25) (17). Since 2010 the onabotulinumtoxin A was approved for chronic migraine prevention by the Food and Drug Administration (FDA) (18). The Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) I and II (NCT00156910, NCT00168428) clinical trials provided the rationale for the approval and the mode and dosage of administration of this neurotoxin in chronic migraine (19-21). Therefore, onabotulinumtoxin A has been the first biological drug for the prevention of chronic migraine. The systematic review and pooled analysis registered in the National Institute for Health Research (NIHR) International prospective register of systematic reviews PROSPERO (CRD42022313640) (22) pointed at the neglected effectiveness of this neurotoxin in an Italian real-world setting, demonstrating that it can improve the efficacy of anti-CGRP/R mAbs in face of good tolerability. In fact, combination therapy consisting in onabotulinumtoxin A associated with mAbs afforded ≥50% reduction of frequency of monthly headache days with respect to onabotulinumtoxin A alone in up to 58.8% of patients and it proved more effective than erenumab, alone or in combination with other preventive drugs (22). Moreover, the treatment with onabotulinumtoxin A is associated to fewer treatment-related adverse events (TRAEs) than oral topiramate, as demonstrated by the systematic review and meta-analysis registered with PROSPERO number CRD42023393250 (23). The findings of the latter also highlight the high heterogeneity of the studies present in the literature (I^2 = 96%; $p < 0.00001$), supporting the need for more, adequately powered, randomized clinical trials.

Discussion and future perspectives

The established efficacy and safety of onabotulinumtoxin A, along with the data gathered so far from real-world and retrospective studies of combination with mAbs, and its complex mechanism of action lend support to the use of this neurotoxin in combination with other drugs able to target the CGRP machinery. In particular, a synergistic/additive effect might involve also other neuromediators, as acetylcholine, glutamate and substance P, the neuronal/Schwann cell pathway (24), and a differential action on Aδ- and not C-fibers (25). Therefore, an adequately powered and designed clinical trial, involving even the elderly, that if affected by cognitive impairment are generally excluded (11, 26-28), is needed to assess the efficacy and safety of the novel approaches of combination therapies targeting the machinery of CGRP and onabotulinumtoxin A. Among the newest therapeutic options for the treatment and prevention of chronic migraine, atogepant, being the first and only oral gepant specifically developed for migraine prevention (29), might represent a very interesting drug to test in combination with onabotulinumtoxin A since it might also afford better compliance to the therapy. Furthermore, novel approaches based on natural products deserve investigation (30-31).

Funding Details: This research is coordinated by DS and received partial financial support from: 1) Phase 2 RIABEO Funding (Executive Decree n.6790 of 22 June 2022) Progetto Ingegno POR Calabria FESR 2014/2020—Azione 1 1 5—Sostegno all'Avanzamento tecnologico delle Imprese Attraverso il Finanziamento di Linee Pilota e Azioni di Validazione Precoce di Prodotti e di Dimostrazione su Larga Scala (DDG N. 12814 DEL 17 October 2019); 2) by the Italian Ministry of Health: NET-2016-02361805 (WP 5).

Disclosure Statement: The authors declare no conflict of interest.

References

1. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808, doi:10.1177/0333102413485658.
2. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain. 2018;19(1):17, doi:10.1186/s10194-018-0846-2.
3. Scuteri D, Adornetto A, Rombolà L, et al. Pattern of triptans use: A retrospective prescription study in Calabria, Italy. Neural regeneration research. 2020;15(7):1340-3, doi:10.4103/1673-5374.272630.
4. Scuteri D, Corasaniti MT, Tonin P, Nicotera P, Bagetta G. Role of CGRP pathway polymorphisms in migraine: a systematic review and impact on CGRP mAbs migraine therapy. The Journal of Headache and Pain. 2021;22(1):87, doi:10.1186/s10194-021-01295-7.
5. Scuteri D, Rombolà L, Tonin P, et al. Genetic variants of CGRP signaling pathway in migraine: impact on novel therapeutics. Confinia Cephalalgica. 2021;31(3).
6. Hunter P. New migraine therapies promise prevention: A new generation of drugs could avert migraine attacks rather than merely relieve symptoms. EMBO reports. 2016;17(6):797-9, doi:10.15252/embr.201642519.
7. Martelletti P, Edvinsson L, Ashina M. Shaping the future of migraine targeting Calcitonin-Gene-Related-Peptide with the Disease-Modifying Migraine Drugs (DMMDs). J Headache Pain. 2019;20(1):60, doi:10.1186/s10194-019-1009-9.
8. Scuteri D, Tonin P, Nicotera P, Bagetta G, Corasaniti MT. Real world considerations for newly approved CGRP receptor antagonists in migraine care. Expert review of neurotherapeutics. 2022;22(3):221-30, doi:10.1080/14737175.2022.2049758.
9. Scuteri D, Tarsitano A, Tonin P, Bagetta G, Corasaniti MT. Focus on zavegepant: the first intranasal third-generation gepant. Pain management. 2022;12(8):879-85, doi:10.2217/pmt-2022-0054.
10. Winner PK, McAllister P, Chakhava, et al. Effects of Intravenous Eptinezumab vs Placebo on Headache Pain and Most Bothersome Symptom When Initiated During a Migraine Attack: A Randomized Clinical Trial. Jama. 2021;325(23):2348-56, doi:10.1001/jama.2021.7665.
11. Scuteri D, Corasaniti MT, Tonin P, Bagetta G. Eptinezumab for the treatment of migraine. Drugs of today (Barcelona, Spain : 1998). 2019;55(11):695-703, doi:10.1358/dot.2019.55.11.3069864.
12. Scuteri D, Bagetta G. Progress in the Treatment of Migraine Attacks: From Traditional Approaches to Eptinezumab. Pharmaceuticals (Basel, Switzerland). 2021;14(9), doi:10.3390/ph14090924.
13. Scuteri D, Adornetto A, Rombolà L, et al. New Trends in Migraine Pharmacology: Targeting Calcitonin Gene-Related Peptide (CGRP) With Monoclonal Antibodies. Frontiers in pharmacology. 2019;10:363, doi:10.3389/fphar.2019.00363.
14. Sandrini G, De Icco R, Tassorelli C, Smania N, Tamburin S. Botulinum neurotoxin type A for the treatment of pain: not just in migraine and trigeminal neuralgia. The Journal of Headache and Pain. 2017;18(1):38, doi:10.1186/s10194-017-0744-z.
15. De Icco R, Perrotta A, Berra E, et al. OnabotulinumtoxinA Reduces Temporal Pain Processing at Spinal Level in Patients with Lower Limb Spasticity. Toxins. 2019;11(6):359.
16. Jianghui M, Saak VO, Jiafu W, et al. Activation of TRPV1 Mediates Calcitonin Gene-Related Peptide Release, Which Excites Trigeminal Sensory Neurons and Is Attenuated by a Retargeted Botulinum Toxin with Anti-Nociceptive Potential. The Journal of Neuroscience. 2009;29(15):4981, doi:10.1523/JNEUROSCI.5490-08.2009.
17. Welch MJ, Purkiss JR, Foster KA. Sensitivity of embryonic rat dorsal root ganglia neurons to Clostridium botulinum neurotoxins. Toxicon. 2000;38(2):245-58, doi:https://doi.org/10.1016/S0041-0101(99)00153-1.
18. David MS, Mark H, Eric JA, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. Neurology. 2016;86(19):1818, doi:10.1212/WNL.0000000000002560.
19. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Results From the Double-Blind, Randomized, Placebo-Controlled Phases of the PREEMPT Clinical Program. Headache: The Journal of Head and Face Pain. 2010;50(6):921-36, doi:https://doi.org/10.1111/j.1526-4610.2010.01678.x.
20. Aurora S, Dodick D, Turkel C, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010;30(7):793-803, doi:10.1177/0333102410364676.
21. Diener H, Dodick D, Aurora S, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010;30(7):804-14, doi:10.1177/0333102410364677.
22. Scuteri D, Tonin P, Nicotera P, et al. Pooled Analysis of Real-World Evidence Supports Anti-CGRP mAbs and OnabotulinumtoxinA Combined Trial in Chronic Migraine. Toxins. 2022;14(8), doi:10.3390/toxins14080529.
23. Corasaniti MT, Bagetta G, Nicotera P, et al. Safety of Onabotulinumtoxin A in Chronic Migraine: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Toxins. 2023;15(5), doi:10.3390/toxins15050332.
24. De Logu F, Nassini R, Hegron A, et al. Schwann cell endosome CGRP signals elicit periorbital mechanical allodynia in mice. Nature Communications. 2022;13(1):646, doi:10.1038/s41467-022-28204-z.
25. Pellesi L, Do TP, Ashina H, Ashina M, Burstein R. Dual Therapy With Anti-CGRP Monoclonal Antibodies and Botulinum Toxin for Migraine Prevention: Is There a Rationale? Headache: The Journal of Head and Face Pain. 2020;60(6):1056-65, doi:https://doi.org/10.1111/head.13843.

26. Bayer A, Tadd W. Unjustified exclusion of elderly people from studies submitted to research ethics committee for approval: descriptive study. Bmj. 2000;321(7267):992-3, doi:10.1136/bmj.321.7267.992.
27. Scuteri D, Adornetto A, Rombolà L, et al. Pattern of triptans use: a retrospective prescription study in Calabria, Italy. Neural regeneration research. 2020;15(7):1340-3, doi:10.4103/1673-5374.272630.
28. Scuteri D, Corasaniti MT, Tonin P, Nicotera P, Bagetta G. Role of CGRP pathway polymorphisms in migraine: a systematic review and impact on CGRP mAbs migraine therapy. J Headache Pain. 2021;22(1):87, doi:10.1186/s10194-021-01295-7.
29. Goadsby PJ, Dodick DW, Ailani J, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. The Lancet Neurology. 2020;19(9):727-37, doi:https://doi.org/10.1016/S1474-4422(20)30234-9.
30. Scuteri D, Rombolà L, Crudo M, et al. Preclinical Characterization of Antinociceptive Effect of Bergamot Essential Oil and of Its Fractions for Rational Translation in Complementary Therapy. Pharmaceutics. 2022;14(2):312. doi: 10.3390/pharmaceutics14020312.
31. Scuteri D, Cassano R, Trombino S, Russo R, Mizoguchi H, Watanabe C, et al. Development and Translation of NanoBEO, a Nanotechnology-Based Delivery System of Bergamot Essential Oil Deprived of Furocumarins, in the Control of Agitation in Severe Dementia. Pharmaceutics. 2021;13(3):379. doi: 10.3390/pharmaceutics13030379.

Correspondence:
Damiana Scuteri
Pharmacotechnology Documentation and Transfer Unit, Preclinical and Translational Pharmacology, Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, 87036 Rende, Italy.
Tel./Fax: +390984/493462;
E-mail: damiana.scuteri@unical.it