# Optimism and Opportunities with Anti-CGRP Biologics in Migraine: Where Are We Today?

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## Meeting Summary

In his opening remarks, Prof Ashina explained the theme behind the Teva-sponsored satellite symposium: to inform the audience about the science behind the emergence of calcitonin gene-related peptide (CGRP) as a target for migraine prevention, the clinical evaluation of anti-CGRP monoclonal antibodies (mAb), including the latest clinical data on fremanezumab leading to its licensure, and the importance of considering the patient experience when initiating anti-CGRP treatment. Prof Ashina also highlighted the greatest unmet needs with respect to current migraine management, ranging from underdiagnosis and underutilisation of preventive therapies,

suboptimal efficacy and tolerability of existing medications, poor adherence, comorbidities, and migraine-related disability. Prof Dickenson introduced the audience to the identification of CGRP as one of the key mediators of migraine pathophysiology and nociception. He then delineated central and peripheral pathways in which CGRP plays a role in the neurovascular processes associated with migraine to show why anti-CGRP interventions hold the promise for better preventive therapies against migraine. Prof Katsarava stated the shortcomings of current preventive therapies and highlighted low adherence to current chronic treatment. He then showcased the clinical data from the HALO and FOCUS trials, which found fremanezumab to be a good candidate for migraine preventive therapy. Finally, Dr Pozo-Rosich discussed the importance of a patient-oriented approach when deciding which is the right treatment for the right patient, noting that this is a component of both personalised and precision medicine. She also added that before evaluating the benefits of or commencing preventive migraine treatment, both the patient perspective and the experience of the physician should be taken into consideration.

## Anti-CGRP Biologics: A New Era for Migraine Prevention

### Professor Anthony Dickenson

Migraine is a complex neurological disorder with an approximate global prevalence of 15%.[1] It is characterised by a moderate-to-severe unilateral headache that is aggravated by routine physical activity and is also generally accompanied by photo and phono-sensitivity, nausea, and vomiting. The impact of migraine on physical, social, and occupational functioning is reflected in it being the leading cause of neurological disability, as well as one of the top five causes of chronic disability.[1,2] While the pathophysiology of migraine is still not fully understood, one of the key mediators involved has been shown to be CGRP, a 37-amino acid peptide primarily localised to the C and A∂ sensory fibres that are widely present in the body and have nociceptive as well as effector functions.[3]

Prof Dickenson began his presentation with a brief timeline of the discovery of CGRP[4,5] and its identification as a potential target for migraine therapy, before proceeding to brief the audience on the neurophysiological basis of migraine and what has been discovered so far. Migraine is thought to be a disorder of sensory processing in the brain, involving both the central and peripheral systems, and characterised by generalised neuronal hyperexcitability.[6] The symptomatology of migraine is complex, suggesting abnormal functioning in multiple neuronal systems, including those in the brain stem and diencephalic regions, which results in premonitory symptoms. The subsequent involvement of the dural trigeminovascular system is manifested as the pain phase of migraine. The central sensitisation hypothesis proposes that altered processing of sensory inputs in the trigeminal nucleus caudalis could account for numerous temporal and symptomatic characteristics of migraine.[7] In addition, peripheral sensitisation is thought to contribute to migraine, especially in conditions in which the threshold for stimulation of the peripheral sensory neurons is reduced,[7] through irritation of peripheral trigeminal fibres by inflammatory mediators,[7,8] or the release of CGRP in the periphery, which can amplify and sustain inflammatory responses. Such conditions are known to also sensitise peripheral nociceptive neurons.[9]

While CGRP is proposed to have various functions in normal physiology and pathology, its role as a vasodilator in the cardiovascular system is well known and there has been a substantial amount of research to explore its somatosensory function in modulation of neuronal sensitisation and pain.[10] Evidence indicates that CGRP is involved in the development of peripheral sensitisation and the enhanced pain associated with it. CGRP has also been found to be upregulated in inflammatory processes and neuropathic pain, hinting at a role in neurogenic inflammation. CGRP is thought to contribute to the development and maintenance of a sensitised neuronal condition at the primary afferent sensory neurons, as well as secondary pain transmission neurons in the central nervous systems, thereby contributing to central sensitisation as well. Such a hypersensitised neuronal state is a key factor underlying migraine pathophysiology.

Prof Dickenson further explained the models postulating the role of CGRP in peripheral and central sensitisation as stated in Iyengar et al.[10] and showed that CGRP is a key signalling molecule at both ends of pain fibres.[11,12] Furthermore, Prof Dickenson shared results published by McCoy et al.[13] which have shown that CGRPα-expressing sensory neurons terminate in the dorsal spinal/trigeminal cord and respond to noxious stimuli that evoke pain and itch sensation.

Given the role played by CGRP in both the central and peripheral processes associated with migraine, Prof Dickenson concluded that mAb targeting CGRP at sites on the dura, the peripheral neurons, or the trigeminal ganglia offer the potential for more effective migraine prevention.

## Changing Pathways, Changing Lives: Taking Control of Migraine Development

### Professor Zaza Katsarava

Depending on their frequency, migraines are classified as episodic or chronic.[14] In episodic migraine, patients experience headache on <15 days per month, while chronic migraine is characterised by ≥15 headache days per month for at least 3 months; with headaches bearing migrainous features for at least 8 of those days in both cases. The pharmacologic treatment of migraine depends on the frequency of headaches and may be either acute (abortive) or preventive (prophylactic).[15] Preventive therapy has been shown to possess numerous benefits. Besides reduction in frequency, duration, and severity of attacks,[15] preventive treatments may also enhance response to acute treatments, reduce patient disability,[16] and even result in reduction of healthcare costs associated with migraine.[17]

Despite established guidelines, a large proportion of patients do not receive preventive therapy, even in developed countries, an issue Prof Katsarava illustrated with the findings of the Eurolight study.[18] In addition, he emphasised the poor adherence to oral preventive treatments in migraine patients.[19] These factors, compounded further by inadequate efficacy and tolerability of current oral preventive therapy for migraine, have driven the search for new treatments. The most promising of which are the CGRP-targeting mAb, which specifically target key pathways in migraine and have an acceptable safety and efficacy profile. Following a series of clinical evaluation programmes, currently three anti-CGRP mAb (erenumab, fremanezumab, and galcanezumab) have been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), while eptinezumab is currently awaiting licensure.[20,21] Prof Katsarava summarised the landmark clinical trials for these mAb, as well as their salient target and pharmacokinetic properties, before proceeding to discuss the results of the HALO trial programme for evaluation of fremanezumab.

HALO EM was a multinational, randomised controlled trial (RCT) conducted across 123 sites in 9 countries between March 2016 and April 2017.[22] The objective of this study was to assess the efficacy of subcutaneous fremanezumab, administered monthly over 12 weeks or as one single higher dose (intended to support quarterly dosing), in preventing episodic migraine attacks in patients in whom multiple migraine medication classes had not previously failed. The study recruited a total of 875 patients (fremanezumab monthly, n=290; fremanezumab quarterly, n=291; placebo, n=294) and the primary endpoint was the mean change from baseline in the monthly average number of migraine days during the 12-week intervention period after the first dose. Results from participants who completed the HALO EM study showed that the least-squares mean reduction in the average number of monthly headache days was 3.9 days with fremanezumab single higher dose (n=288), 4.0 days with fremanezumab monthly (n=287), and 2.6 with placebo (n=290) ($p<0.001$ for both comparisons with placebo). Moreover, in comparison to those receiving placebo, patients in the fremanezumab groups had a decrease in the monthly average number of migraine days, with both monthly dosing (difference: -1.5 days; 95% confidence interval [CI]: -2.01 to -0.93 days; $p<0.001$) and the single dose (difference: -1.3 days; 95% CI: -1.79 to -0.72 days; $p<0.001$) regimens. In addition, the proportion of patients achieving a reduction of ≥50% in the monthly number migraine days over 12 weeks with fremanezumab monthly, fremanezumab single higher dose, and placebo was 47.7%, 44.4%, and 27.9%, respectively ($p<0.001$ for both fremanezumab doses versus placebo).

HALO CM was a multinational RCT conducted across 132 sites in 9 countries between March 2016 and January 2017.[23] Similarly to HALO EM, the objective of this study was to assess the efficacy of subcutaneous fremanezumab, administered quarterly or monthly over 12 weeks, in preventing chronic migraine. The study recruited 1,130 patients (fremanezumab quarterly, n=376; fremanezumab monthly, n=379; placebo, n=375) and the primary endpoint was the mean change from baseline in the average number of monthly headache days of at least moderate severity during the 12-week intervention period. In those who completed the trial, the least-squares mean (±standard error) reduction in the average number of monthly headache days was 4.3 (±0.3) with fremanezumab quarterly (n=375), 4.6 (±0.3) with fremanezumab monthly (n=375), and 2.5 (±0.3) with placebo (n=371) ($p<0.001$ for both comparisons with placebo). In addition, the proportion of patients achieving ≥50% reduction in the monthly number of headache days of at least moderate severity over 12 weeks for fremanezumab quarterly, fremanezumab monthly, and placebo was 38%, 41%, and 18%, respectively ($p<0.001$ for both fremanezumab doses versus placebo).

Having detailed the findings of the HALO trials, Prof Katsarava emphasised the need for long-term efficacy and safety data to inform decision-making before introducing data from the HALO Long-Term Study, which had recently been presented at the 13th European Headache Federation (EHF) Congress 2019 in Athens, Greece. These data showed sustained reductions in the average number of monthly migraine days over 12 months in patients with both episodic and chronic migraine.[24] In addition, the average number of patients with episodic and chronic migraine who achieved a reduction of ≥50% in the average number of monthly migraine days was sustained.[25] Prof Katsarava then proceeded to share unpublished data from the FOCUS study, an RCT that assessed the efficacy of monthly or quarterly fremanezumab over 24 weeks in difficult-to-treat patients, defined as those with episodic and chronic migraine who had previously failed to respond to 2–4 classes of preventive treatment. Results from the FOCUS study not only reiterate previous findings by showing a significant reduction in the average number of monthly migraine days in fremanezumab-treated patients compared with placebo,[26] but also showed a rapid change in the average number of weekly migraine days[27] and a decrease in the use of acute headache medication in the fremanezumab groups.[26] In addition, fremanezumab demonstrated a favourable long-term safety and tolerability profile with low treatment discontinuation rate due to adverse events.

Prof Katsarava concluded his presentation by summarising the acceptable safety and efficacy of anti-CGRP therapies and their advantages for use as preventive treatment for migraine.

## The Right Treatment for the Right Patients

### Doctor Patricia Pozo-Rosich

Multiple evidence-based guidelines recommend preventive therapy as part of the overall approach to migraine management. Preventive treatment is especially recommended for patients with frequent attacks (starting at ≥4 monthly headache days); patients in whom migraine substantially interferes with daily activities despite acute treatment; or those in whom acute treatments are contraindicated, ineffective, or lead to overuse.[15,28-30] Because the currently available oral preventive treatments were not designed for treating migraine, they offer a suboptimal efficacy and tolerability profile, and their use is limited by contraindications and drug interactions.[30] These factors may explain why the proportion of migraine patients who use preventive therapies is low, despite many being candidates for a preventive approach.[31,32] To optimise use of preventive therapy, it is necessary to individualise treatment based on severity and frequency of attacks, presence of other comorbidities and associated symptoms, type and severity of disabilities, contraindications and concomitant medications, and just as importantly, patient preference.

Dr Pozo-Rosich's presentation focussed on the importance of taking into account the patient perspective when considering preventive treatments for migraine. The common goal of migraine treatment, from the physician's and patient's perspectives, is to improve patient

quality of life and minimise disease burden. Hence, the choice of the intervention needs to be viewed from both these perspectives for it to be successful. Dr Pozo-Rosich stated that while personalised medicine allows for this to some extent, this process needs to be fine-tuned by improving patient–physician communication and practicing precision medicine. Patient factors, such as demographics, age, sex, and diagnosis are usually taken into account by the treating physician when recommending particular preventive treatments in migraine; however, other factors, such as lifestyle and work, the presence of comorbidities, and response to previous treatments, also need to be taken into account in selecting an appropriate treatment.

Dr Pozo-Rosich further stated that this approach of acknowledging the patient perspective needs to be implemented at the clinical evaluation phase to identify patient factors that could have a bearing on the appropriateness of preventive treatments. Moreover, besides objective diagnosis based on clinical evaluations, physicians also need to take into consideration how patients feel about prescribed treatments despite this being a subjective issue. To illustrate this, Dr Pozo-Rosich first presented data from a study by Mitsikostas et al.,[33] which evaluated patient preferences in the acute and preventive treatment of headaches. When study patients were asked whether safety, efficacy, or route of administration were important to them with respect to symptomatic treatment, >80% of the patients with migraine listed efficacy as the factor most important to them. Gathering such feedback from patients is essential in understanding the factors that they regard as important in their treatment. While direct face-to-face communication is helpful in understanding these, this process could be improved by the use of standardised algorithms to gather patient-reported outcomes (PRO). Though PRO are useful in gauging patient perception, numerous factors such as the appropriateness of an outcome being reported need to be examined when designing the PRO questionnaire. To demonstrate this, Dr Pozo-Rosich listed the various instruments used to collect PRO during the clinical evaluation of CGRP mAb,[34] as well as data from the fremanezumab trial programme, which could be evaluated according to patient factors such as age, sex,[35] diagnosis,[36] and even comorbidities, such as depression.[37] Dr Pozo-Rosich added that although these data give us some insights into the influence of some patient factors, there remains much to be learned. One key approach would be to find better ways of evaluating what the term 'efficacy' means for each patient in order to first choose a preventive treatment, and then evaluate whether the treatment is effective or not before deciding about continuing or stopping treatment.

Dr Pozo-Rosich concluded her presentation by reiterating the importance of harmonising the patient–physician perspectives and stating that, in the future, prognostic factors will need to be defined in order to ensure that "the right treatment is offered to the right patient at the right time."

## Conclusion

CGRP plays a key role in the peripheral and central pain mechanisms involved in migraine and its chronification. Hence, CGRP is a rational target for designing biological or chemical agents for migraine prevention. The discovery of mAb that bind either CGRP or its receptor, and subsequently prevent the activation of downstream pathways that are intrinsic to migraine, offer improved outcomes for those with both episodic and chronic migraine. Phase III trials with anti-CGRP mAb have shown promising results with a reduction in the number of migraine days and use of acute migraine medications, a rapid onset of action for some patients, and an acceptable safety profile. The successful integration of anti-CGRP biologics in preventive treatment of migraine will rely on adopting a precision medicine approach in the informed clinical decision-making process where patient preferences will also be taken into account.

## References


1. Steiner TJ et al. Migraine: The seventh disabler. J Headache Pain. 2013;14(1):1.
2. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211-59.
3. Russell FA et al. Calcitonin gene-related peptide: Physiology and pathophysiology. Physiol Rev. 2014;94(4):1099-142.
4. Rosenfeld MG et al. Production of novel neuropeptide encoded by the calcitonin gene via tissue-specific RNA processing. Nature. 1983;304(5922):129-35.
5. McCulloch J et al. Calcitonin gene-related peptide: Functional role in cerebrovascular regulation. Proc Natl Acad Sci U S A. 1986;83(15):5731-5.
6. Akerman S et al. Current and novel insights into the neurophysiology of migraine and its implications for therapeutics. Pharmacol Ther. 2017;172:151-79.
7. Dodick D, Silberstein S. Central sensitization theory of migraine: Clinical implications. Headache. 2006;46(Suppl 4):S182-91.
8. Strassman AM et al. Sensitization of meningeal sensory neurons and the origin of headaches. Nature. 1996;384(6609):560-4.
9. Schlereth T, Birklein F. The sympathetic nervous system and pain. Neuromuscular Med. 2008;10(3):141-7.
10. Iyengar S et al. The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. Pain. 2017;158(4):543-59.
11. Todd AJ. Neuronal circuitry for pain processing in the dorsal horn. Nat Rev Neurosci. 2010;11(12):823-36.
12. Usoskin D et al. Unbiased classification of sensory neuron types by large-scale sing-cell RNA sequencing. Nat Neurosci. 2015;18(1):145-53.
13. McCoy ES et al. CGRPa-expressing sensory neurons respond to stimuli that evoke sensations of pain and itch. PLoS One. 2012;7(5):e36355.
14. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). Cephalalgia. 2013:33:629-808.
15. Silberstein SD. Preventive migraine treatment. Continuum (Minneap Minn). 2015;21(4 Headache):973-89.
16. Lipton RB, Silberstein SD. Why study the comorbidity of migraine? Neurology. 1994;44(10 Suppl 7):S4-5.
17. Silberstein SD et al. Migraine preventive medication reduces resource utilization. Headache. 2003;43(3):171-8.
18. Katsarava Z et al. Poor medical care for people with migraine in Europe – Evidence from the Eurolight study. J Headache Pain. 2018;19(1):10.
19. Hepp Z et al. Adherence to oral migraine-preventative medications among patients with chronic migraine. Cephalalgia. 2015;35(6):478-88.
20. Mitsokostas DD, Reuter U. Calcitonin gene-related peptide monoclonal antibodies for migraine prevention: comparisons across randomized controlled studies. Curr Opin Neurol. 2017;30(3):272-80.
21. Edvinsson L et al. CGRP as the target of new migraine therapies – Successful translation from bench to clinic. Nat Rev Neurol. 2018;14(6): 338-50.
22. Dodick DW et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: A randomized controlled trial. JAMA. 2018;319(19):1999-2008.
23. Silberstein SD et al. Fremanezumab fort the preventative treatment of chronic migraine. N Eng J Med. 2017;377(22):2113-22.
24. Goadsby PJ et al. Long-term efficacy and safety of fremanezumab in migraine: Results of a 1-year study. e-Poster 015. Presented at the 13th EHF Congress, Athens, Greece, 30 May - 1 June 2019.
25. Newman LC et al. Long-term impact of fremanezumab on response rates: Results of a 1-year study. e-Poster 010. Presented at the 13th EHF Congress, Athens, Greece, 30 May - 1 June, 2019.
26. Ferrari MD et al. Efficacy and safety of fremanezumab in patients in migraine and documented inadequate response to 2 to 4 classes of migraine preventive treatments: results of the international, multicentre, randomised, placebo-controlled FOCUS study. Presented at 13th EHF Congress. Athens, Greece, 30 May - 1 June, 2019.
27. Spierings ELH et al. Early onset of response to fremanezumab in patients with migraine and a documented inadequate response to 2–4 classes of migraine preventive treatments: Results of the international, multicentre, randomised, placebo-controlled FOCUS study. e-Poster 022. Presented at the 13th EHF Congress, Athens, Greece, 30 May - 1 June, 2019.
28. Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000;55(6):754-62.
29. Dodick DW, Silberstein SD. Migraine prevention. Pract Neurol. 2007;7(6):383-93.
30. Hepp Z et al. Comparative effectiveness of onabotulinumtoxinA versus oral migraine prophylactic medications on headache-related resource utilization in the management of chronic migraine: Retrospective analysis of a US-based insurance claims database. Cephalagia. 2016;36(9):862-74.
31. Lipton RB et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-9.
32. Blumenfeld AM et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: Results from the second international burden of migraine study (IBMS-II). Headache. 2013;53(4):644-55.
33. Mitsikostas DD et al. Patients' preferences for headache acute and preventative treatment. J Headache Pain. 2017;18(1):102.
34. Torres-Ferrus M et al. How much do calcitonin gene-related peptide monoclonal antibodies improve the quality of life in migraine? A patient's perspective. Curr Opin Neurol. 2019;32(3):395-404.
35. Maassen van den Brink A et al. Impact of age and sex on efficacy of fremanezumab in patients with migraine and documented inadequate response to 2 to 4 classes of migraine preventive treatments: results of the international, multicentre, randomised, placebo-controlled FOCUS study. Presented at 13th EHF Congress. Athens, Greece, 30 May - 1 June, 2019.
36. Cohen J et al. Long-term impact of fremanezumab on headache-related disability, quality of life, and patient satisfaction in episodic migraine and chronic migraine. Presented at 13th EHF Congress. Athens, Greece, 30 May - 1 June, 2019.
37. Lipton RB et al. Long-term efficacy of fremanezumab in patients with chronic migraine and comorbid moderate to severe depression. e-Poster 012. Presented at the 13th EHF Congress, Athens, Greece, 30 May - 1 June, 2019.