Nordic Migraine Symposium 20

Summary Report

Migraine Management

Looking Ahead

2nd Nordic Migraine Symposium, 27–28 November 2020

Teva Norway AS/03.2021

teva

Cosponsor:

WILEY

This Symposium Report was published by John Wiley & Sons Ltd, in association with and with sponsorship from Teva Nordic Medical Affairs AS.

This Report highlights the presentations that were held during the Nordic Migraine Symposium 2020, sponsored by Teva Nordic Medical Affairs, which was held on 27 and 28 November 2020 in Oslo.

Medical Writer
Steve Chaplin

Design and Layout
Michael Smith

Publisher
John Wiley & Sons Ltd
The Atrium,
Southern Gate
Chichester
West Sussex,
PO19 8SQ, UK

WILEY

Sponsor

teva

Teva Norway AS
Kinoveien 3A,
1337 Sandvika,
Norway

Unmet needs in migraine management

Jan Versijpt,
MD, PhD Neurologist, UZ Brussel, Belgium

Migraine management is not fully meeting the needs of patients and clinicians in three important areas: the role of monoclonal antibodies targeting CGRP, understanding the clinical role of neuromodulation and the development of biomarkers for migraine.

Monoclonal antibodies against CGRP are by far the most exciting development in the treatment of migraine since the triptans. Several Phase III randomised controlled trials have provided definitive evidence of efficacy and tolerability. Real-world studies are now being reported[1] that will provide the evidence of long-term safety and data needed to develop pharmacoeconomic analyses. As health services adapt to the post-Covid-19 era, this is particularly important for the anti-CGRP monoclonal antibodies.

We cannot take safety for granted. For example, the association of hypertension with erenumab treatment was recognised only recently, leading to the amendment of prescribing information in the United States (though not, to date, in Europe). It is, however, not a minor point: the development of anti-CGRP monoclonal antibodies was partly driven by the need for a treatment with a lower cardiovascular risk than the triptans.

Several neuromodulation strategies have been evaluated in the treatment and prevention of migraine (Figure 1).

Despite several trials of neuromodulation, its role in migraine management is unclear and there is uncertainty about its place in relation to drug therapy. The design of clinical trials of this intervention is very challenging – it is difficult to be sure that a 'sham' arm truly has no therapeutic effect: the PREMIUM trial of non-invasive vagus nerve stimulation in patients with episodic migraine showed that a sham intervention inadvertently stimulated the vagus nerve. As a result, there was no significant difference between the two arms in the primary endpoint of reduction in migraine days.[2] There is a need for an innovative design that will overcome this obstacle.

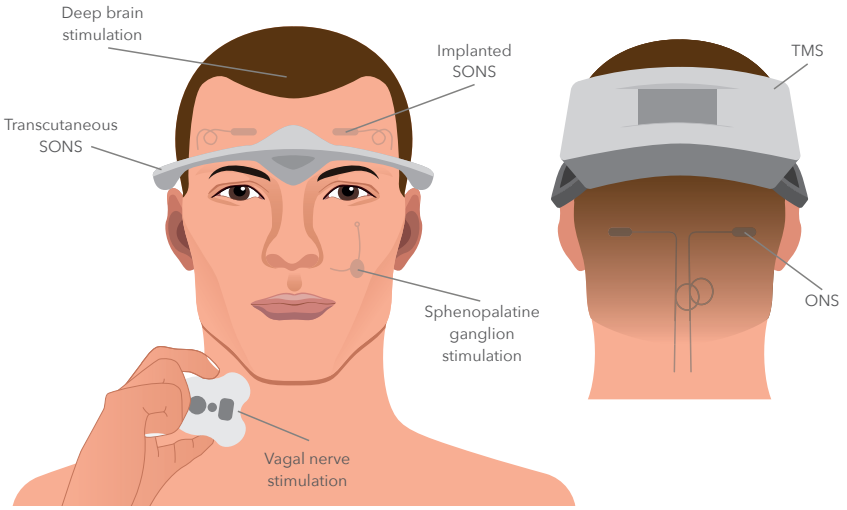

Figure 1 Neuromodulation strategies to treat or prevent migraine

A 2013 review concluded that, in contrast with advances in other therapeutic areas, there were 'no currently accepted biomarkers for chronic or episodic migraine'.[3] The authors suggested that ongoing research would improve diagnosis and treatment but we still have no clinically useful genetic, imaging or laboratory biomarkers for migraine.

There have been promising candidates. Interictal CGRP in peripheral blood is raised in people with untreated chronic migraine but not in controls or individuals with episodic migraine or cluster headache (Figure 2).[4] Unfortunately, the assay for CGRP is difficult to perform and this has limited its development as a biomarker for clinical use.

In light of this experience, there is a case for valuing clinical skills more than we do and exploring the relationships between the clinical features of migraine and outcomes. Phenotyping is consistent with the proposed definition of a biomarker as 'An objectively measurable substance, characteristic, or other parameter of a biological process that enables assessment of disease risk or prognosis and provides guidance or monitoring of treatment.'[5] For example, it has recently been shown that specific features of a migraine attack, either before or during the pain phase, correlate with

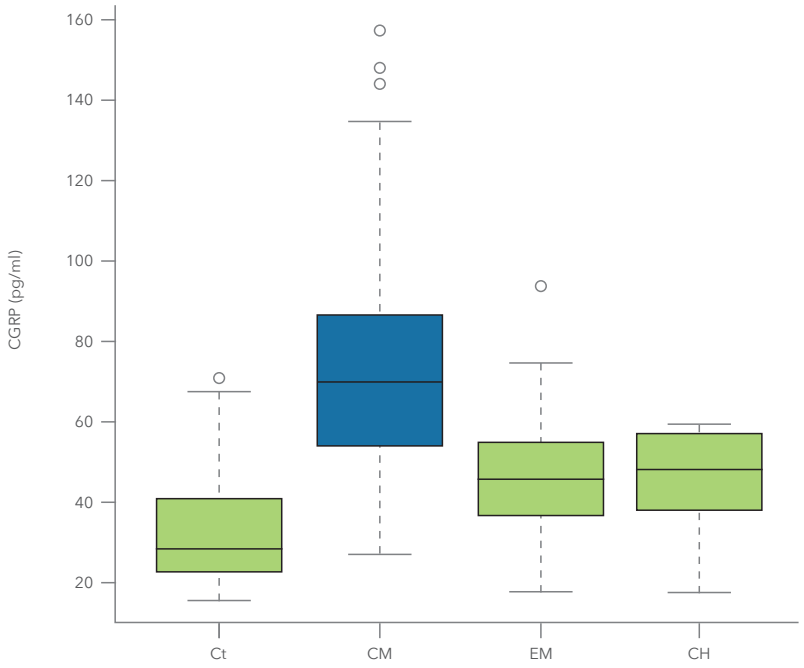

Figure 2 Interictal CGRP is raised in patients with chronic migraine (CM) but not in controls (Ct) or those with episodic migraine (EM) or cluster headache (CH)[4]

the clinical response to frovatriptan: the response to treatment (pain free at 2 hours) was associated with unilateral pain, phonophobia, one or more cranial autonomic symptoms and one or more premonitory symptoms.[6]

In recognising the potential of phenotyping, it is important to remember that migraine classification is a dynamic process and diagnostic labels are not set in stone. There is room for improvement in phenotyping migraine with brainstem aura and retinal migraine (which may not be considered as truly migraine), and chronic migraine with continuous pain.

References

1. Alex A, Vaughn C, Rayhill M. Safety and tolerability of 3 CGRP monoclonal antibodies in practice: a retrospective cohort study. Headache. 2020;60:2454-2462.
2. Diener HC, Goadsby PJ, Ashina M, et al. Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: the multicentre, double-blind, randomised, sham-controlled PREMIUM trial. Cephalalgia. 2019;39:1475-1487.
3. Durham P, Papapetropoulos S. Biomarkers associated with migraine and their potential role in migraine management. Headache. 2013;53:1262-77.
4. Cernuda-Morollón E, Larrosa D, Ramón C, et al. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. Neurology. 2013;81:1191-6.
5. Frisoni GB, Boccardi M, Barkhof F, et al. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. Lancet Neurol. 2017;16:661-676.
6. Viana M, Sances G, Terrazzino S, et al. Predicting the response to a triptan in migraine using deep attack phenotyping: a feasibility study. Cephalalgia. 2020:333102420959786. doi: 10.1177/0333102420959786.

Calcitonin family of peptides in migraine - beyond the CGRP

Hashmat Ghanizada,
MD and PhD Fellow, Danish Headache Center, Rigshospitalet, Glostrup, Denmark

CGRP is one of a family of peptides which share varying degrees of affinity with their receptors. Treatments to prevent migraine are not effective in all patients; this may be due to the effects of other calcitonin peptides in the trigeminal ganglion, including amylin and adrenomedullin.

CGRP, a potent vasodilator and neuromodulator, is one of a family of five calcitonin peptides with multiple biological and pharmacological properties that includes amylin, a satiety hormone expressed mainly in the pancreas; calcitonin itself, which is produced by thyroid C cells to reduce plasma calcium and promote bone formation; and adrenomedullin and adrenomedullin 2, which are potent vasodilators expressed by endothelial cells.[1]

These peptides are structurally similar, with high and sometimes complete homology for some amino acid sequences,[2] and their receptors are expressed in the trigeminal ganglion.[3]

There is cross-reactivity between these peptides and receptors - for example, the AMY1 receptor is also a receptor for CGRP[4] (Figure 1) – though few are expressed in structures associated with migraine pathogenesis and the role, if any, of the AMY1 receptor in migraine is still under investigation.

Migraine is, to the best of our knowledge, a solely human experience. Infusion of CGRP evokes immediate and delayed migraine attacks in 60–75% of people with migraine.[5] There are now three monoclonal antibodies against the CGRP ligand licensed for migraine prevention (eptinezumab, fremanezumab, galcanezumab) and one targeting the CGRP receptor itself (erenumab). Clinical trials have reported response rates (50% reduction in monthly headache days) of approximately 40–75%.[6] How do we explain this heterogeneity?

It is likely that peptide receptors in the trigeminal ganglion other than the CGRP receptor, and peptides other than CGRP that have a weak affinity for the CGRP receptor, contribute to the pathogenesis of migraine. Monoclonal antibodies targeting CGRP or its receptor therefore do not fully block migraine pathways. Our research, as yet unpublished, has shown that infusion of amylin or adrenomedullin can provoke a migraine attack that mimics spontaneous migraine.

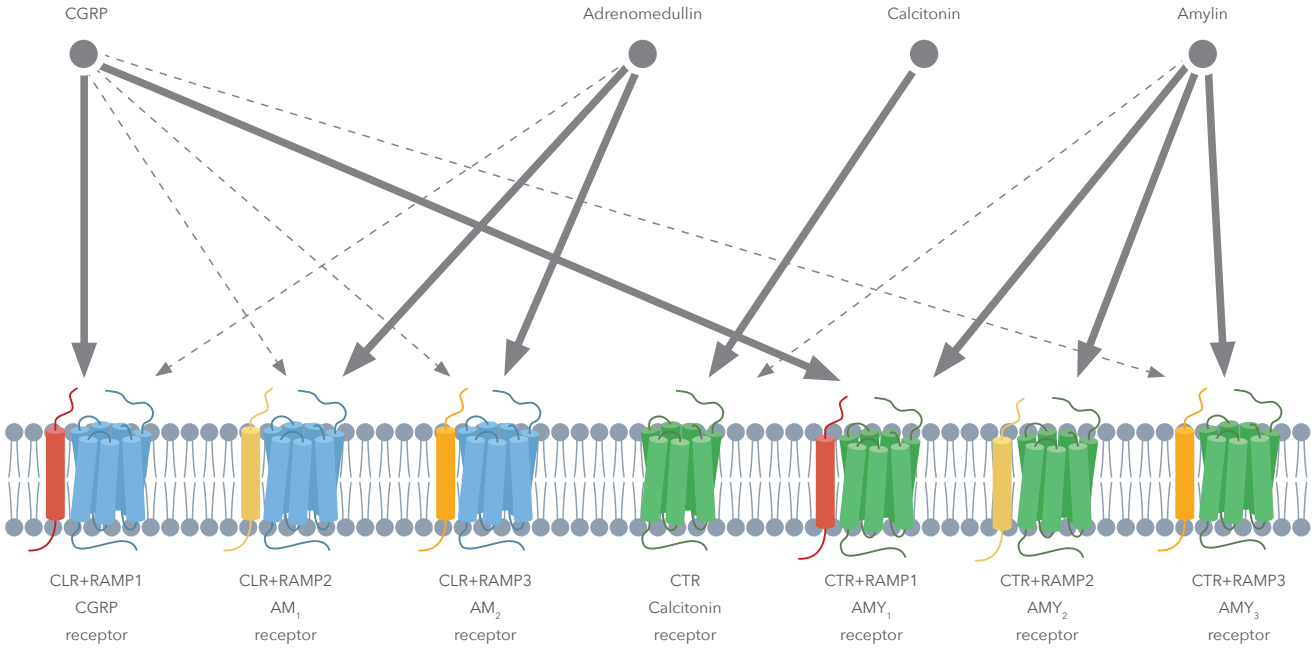

Figure 1 Cross reactivity between CGRP peptides and their receptors in the trigeminal ganglion.
Figure created using data from IUPHAR/BPS Guide to Pharmacology (https://www.guidetopharmacology.org)

This raises the possibility of new therapeutic targets, such as the amylin receptor AMY1 and adrenomedullin receptors AM1 and AM2.

In conclusion, administration of peptides other than CGRP are known to induce migraine, demonstrating that migraine is not a disorder of CGRP but one that appears to involve dysregulation of several peptides and their receptors at different levels of the trigeminovascular pathway.

References

1. Hay DL, Garelja ML, Poyner DR, Walker CS. Update on the pharmacology of calcitonin/CGRP family of peptides: IUPHAR Review 25. Br J Pharmacol. 2018;175:3-17.
2. Garelja ML, Au M, Brimble MA, et al. Molecular mechanisms of Class B GPCR activation: insights from adrenomedullin receptors. ACS Pharmacol Transl Sci. 2020;3:246-262.
3. Edvinsson L, Grell AS, Warfvinge K. Expression of the CGRP family of neuropeptides and their receptors in the trigeminal ganglion. J Mol Neurosci. 2020;70:930-944.
4. Walker CS, Eftekhari S, Bower RL, et al. A second trigeminal CGRP receptor: function and expression of the AMY1 receptor. Ann Clin Transl Neurol. 2015;2:595-608.
5. Ashina M, Hansen JM, Á Dunga BO, et al. Human models of migraine - short-term pain for long-term gain. Nat Rev Neurol. 2017;13:713-724.
6. Charles A, Pozo-Rosich P. Targeting calcitonin gene-related peptide: a new era in migraine therapy. Lancet. 2019;394:1765-1774.

Role of ion channels in the trigeminal system - relation to CGRP signalling

Lars Edvinsson,
MD, DMSci Professor, of Internal Medicine, Lund University, Lund, Sweden, and Copenhagen University, Denmark

CGRP appears to induce pain by modulating the activity of Aδ fibres at the nodes of Ranvier, where they occur in close proximity to C fibres. It is likely that CGRP induces cAMP and protein kinase A (PKA), resulting in inhibition/activation of K^+ channels. This may offer a new therapeutic target for future migraine treatments.

According to the current model of the pathogenesis of migraine, the stimulus for a migraine attack originates in the hypothalamus, activating the trigeminal nucleus caudalis. In turn, this activates the trigeminal ganglion, causing the release of CGRP and resulting in the perception of headache pain. Because antibodies do not normally cross the blood brain barrier, the origin of pain sensitisation is peripheral rather than central, and probably lies in the trigeminovascular system.[1]

Two sensory nerve types in the trigeminovascular system are important in the perception of pain: C and Aδ fibres. Slowly conducting non-myelinated C fibres store and release CGRP, which binds to receptors expressed by fast-conducting, thinly myelinated Aδ fibres.[2] Preventing the release of CGRP from C fibres mitigates migraine pain: for example, triptans inhibit the release of CGRP and, in Aδ fibres, the increase in cAMP induced by the interaction of CGRP with its receptor (Figure 1).

By contrast, agents that raise cAMP in Aδ fibres provoke a migraine attack in patients with migraine. These events occur at the ganglionic level.[3] However, it is not fully understood how activation of the trigeminal nucleus caudalis causes C fibres to release CGRP. Monoclonal antibodies that target CGPR or the CGRP receptor on Aδ fibres do not inhibit the release of CGRP by C fibres but its actions.[4]

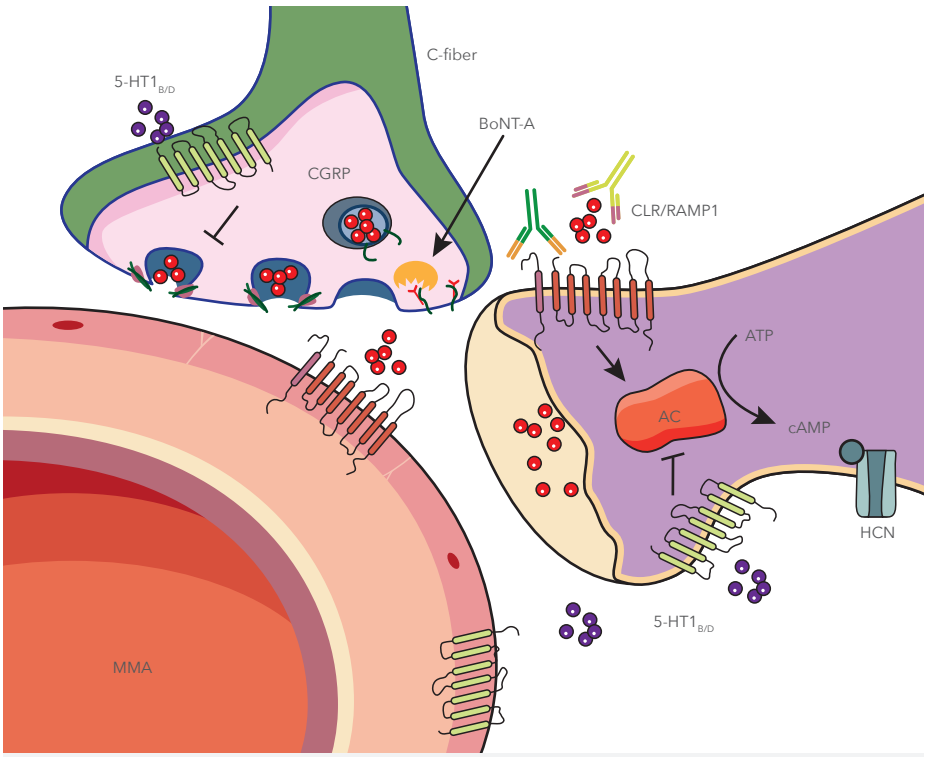

Figure 1 Current model of migraine pain.
Source: Haanes 2019, figure 1, p. 526. Reproduced with permission of Springer Nature

It is well established that CGRP is released from the dura mater and the trigeminal ganglion but where exactly do anti-CGRP monoclonal antibodies act? Saltatory conduction in Aδ fibres occurs when the action potential jumps between the demyelinated nodes of Ranvier. C fibres have pearl-like synaptic structures known as 'boutons' that stain positive for CGRP; these occur adjacent to the nodes of Ranvier where CGRP receptors occur (Figure 2).[5]

These findings suggest that the nodes of Ranvier may be the point of axon-axon interaction within the trigeminal system and ganglion where C fibres can modulate Aδ fibres signalling, and the site where CGRP acts. This generates cAMP in the Aδ fibre, in turn activating protein kinase A which then probably alters the conductance of potassium ion channel on the juxtaparanodal region of the node of Ranvier. The site of action of

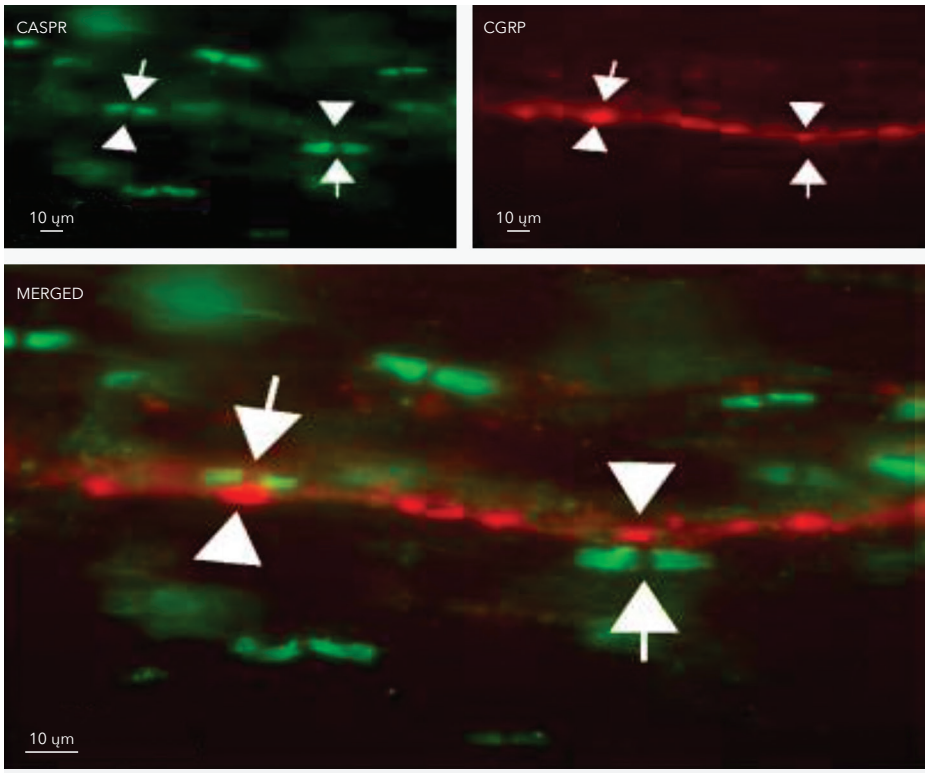

Figure 2 Immunohistochemistry demonstrating co-localisation of the CGRP receptor (denoted by the marker CASPR) in Aδ fibres and CGRP (red) C fibres. Note the gap (in green) identifying the node of Ranvier.[5]
Source: Edvinsson 2019, figure 4, p. 6. Reproduced with permission of BMC

anti-CGRP monoclonal antibodies may therefore be the nodes of Ranvier; if confirmed, this could offer a new target for migraine treatment.

References

1. Lundblad C, Haanes KA, Grände G, et al. Experimental inflammation following dural application of complete Freund's adjuvant or inflammatory soup does not alter brain and trigeminal microvascular passage. J Headache Pain. 2015;16:91. doi: 10.1186/s10194-015-0575-8.
2. Haanes KA, Edvinsson L. Pathophysiological mechanisms in migraine and the identification of new therapeutic targets. CNS Drugs. 2019;33:525-537.
3. Zhang L, Kunkler PE, Knopp KL, et al. Role of intraganglionic transmission in the trigeminovascular pathway. Mol Pain. 2019;15:1744806919836570. doi: 10.1177/1744806919836570.
4. Melo-Carrillo A, Strassman AM, Nir RR, et al. Fremanezumab - A humanized monoclonal anti-CGRP antibody-inhibits thinly myelinated (Aδ) but not unmyelinated (C) meningeal nociceptors. J Neurosci. 2017;37:10587-10596.
5. Edvinsson JCA, Warfvinge K, Krause DN, et al. C-fibers may modulate adjacent Aδ-fibers through axon-axon CGRP signaling at nodes of Ranvier in the trigeminal system. J Headache Pain. 2019;20:105. doi: 10.1186/s10194-019-1055-3.

Migraine patients with medication overuse can be treated with anti-CGRP monoclonal antibodies without withdrawal

Hans Christopher Diener,
Professor of Neurology and Chairman of the Department of Neurology, University Duisberg-Essen, Germany

A 2019 review of the prevention and treatment of medication overuse headache recommended that treatment for migraine attacks should be withdrawn, eliminating the use of acute medication for 2–4 weeks, reducing the frequency of acute medication to less than 2 days per week and switching from triptans or combination analgesics to NSAIDs.[1] This, in light of what is now known about the efficacy safety of the anti-CGRP monoclonal antibodies, is outdated advice.

The Phase III trials of anti-CGRP monoclonal antibodies in the treatment of episodic and chronic migraine included large numbers of patients with medication overuse (MO) and medication overuse headache (MOH). Outcomes for these subgroups have now been described in post hoc analyses. These findings should be interpreted cautiously because the studies were not primarily designed to measure these outcomes and patients with MO or MOH were not managed according to current practice (counselling and discontinuing medication). However, the data suggest that anti-CGRP monoclonal antibodies offer favourable outcomes and a new treatment option for these patients.

The efficacy and safety of fremanezumab were assessed in HALO studies, comprising a 12-week study in patients with chronic migraine (HALO CM)[2] and a 12-month study in patients with episodic migraine (HALO EM).[3] In addition, the FOCUS trial, a 12-week randomised, double-blind study, compared quarterly and monthly fremanezumab and placebo in patients with episodic or chronic migraine.[4] All studies defined MO as ≥15 days using any acute medications or ≥10 days using triptans or ergots; patients taking opioids were excluded.

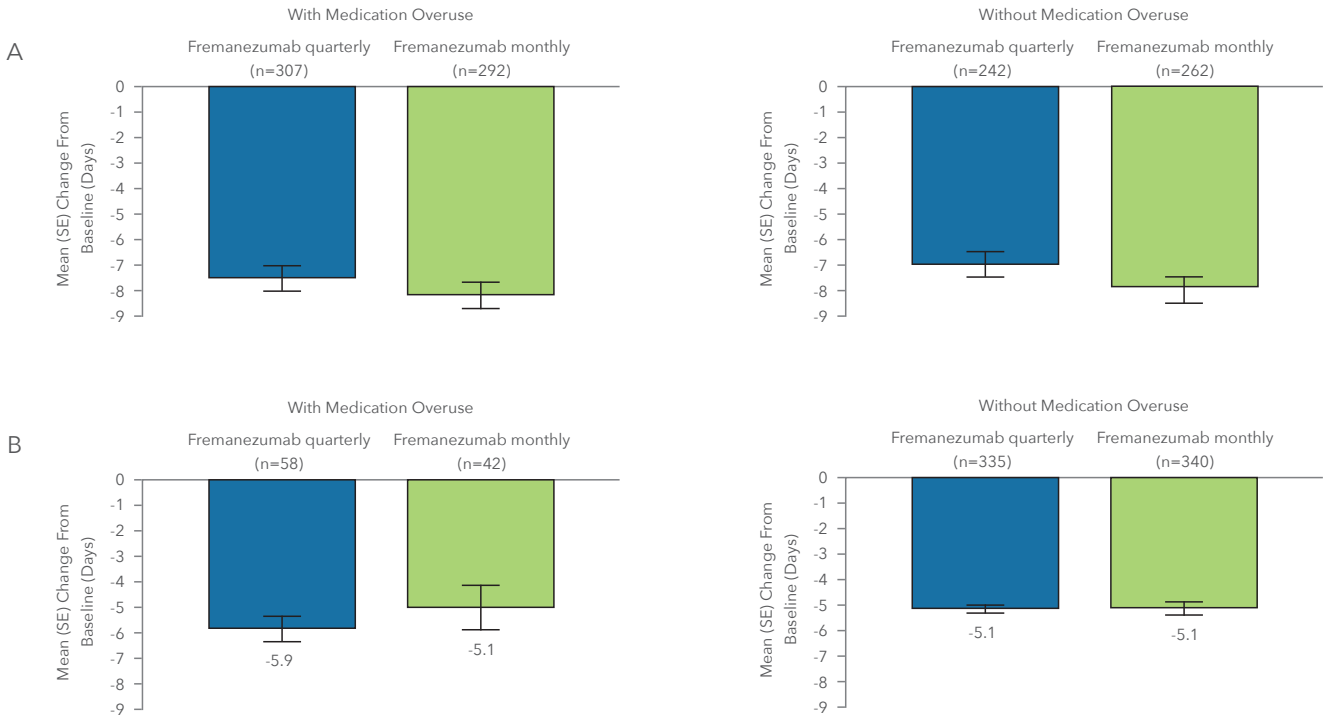

Figure 1 Change in mean monthly number of migraine days in (A) patients with CM and (B) patients with EM at month 12 with or without MO at baseline in the HALO trials[2,3]. Figure created from data in Silberstein 2019 and Siberstein 2020

These analyses showed that, in this difficult to treat group of patients, fremanezumab significantly reduced headache/migraine days and acute medication use, and increased the proportion of patients with ≥50% reduction in mean monthly migraine days and the percentage reverting to non-MO status after 3 and 12 months compared with placebo.

Overall, the mean reduction in migraine days after 12 months was similar for quarterly and monthly fremanezumab and in patients with or without MO at baseline (Figure 1).

The FOCUS study included patients with chronic or episodic migraine with difficult-to-treat migraine in whom treatment with 2–4 classes of preventive medication had failed. In the subgroup with MO at baseline, monthly and quarterly administration fremanezumab significantly reduced monthly migraine days compared with placebo.

A post hoc analysis of the EVOLVE-1 and -2 and REGAIN trials of galcanezumab in patients with episodic or chronic migraine reported similar findings in the subgroups of patients with MO.[5] In patients with episodic migraine, the difference compared with placebo was again greater in patients with MO than those without MO. Overall, galcanezumab reduced monthly headache days compared with placebo in patients with episodic or chronic migraine and significantly increased the proportion of patients with ≥50% reduction in headache/migraine days and reduced the mean number of days using headache medication regardless of MO status.

Similarly, erenumab reduced monthly migraine days and migraine-specific acute medication days significantly more than placebo in patients with MO in whom previous treatment had failed (including triptans and ergot derivatives).[6] This difference was greater than was achieved in patients without MO and was associated with greater proportions of patients reverting to non-MO status for simple analgesics, triptans and combination analgesics.

These analyses were post hoc and patients with MOH were not always prospectively identified but their findings do highlight the need to reconsider the recommendations of current management guidance. Anti-CGRP monoclonal antibodies should be offered as treatment options alongside topiramate and onabotulinum toxin A in the treatment of MOH.

References

1. Diener HC, Dodick D, Evers S, et al. Pathophysiology, prevention, and treatment of medication overuse headache. Lancet Neurol. 2019;18:891-902.
2. Silberstein SD, Cohen JM, Seminerio MJ, et al. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. J Headache Pain. 2020;21:114. doi: 10.1186/s10194-020-01173-8.
3. Silberstein SD, Kudrow D, Cohen JM, et al. Long-term impact of fremanezumab on response rate, acute headache medication use, and disability in episodic migraine patients with acute medication overuse at baseline: results of a 1-year study. Headache 2019;59 Suppl 1:113-114. Abstract P141.
4. Ferrari MD, Diener HC, Spierings EL, et al. Efficacy, clinically meaningful responses, and impact on acute headache medication use with fremanezumab in patients with migraine and documented inadequate response to 2–4 classes of migraine preventive treatments: results of the international, multicentre, randomised, placebo-controlled FOCUS study. J Headache Pain 2020;21:43. Abstract A.59.
5. Aurora SK, Ruff D, Pearlman EM. Medication overuse in a post-hoc analysis of Phase 3 placebo-controlled studies of galcanezumab in the prevention of episodic and chronic migraine. Headache 2019;59 Suppl S1:23. Abstract IOR07.
6. Tepper SJ, Diener HC, Ashina M, et al. Efficacy of erenumab for the treatment of patients with chronic migraine in presence of medication overuse. Cephalalgia 2017;37 Suppl 1: abstract EP-01-013.

Migraine patients can be treated with anti-CGRP monoclonal antibodies after withdrawal: to stop or not to stop that is the question

Rigmor Højland Jensen,
Dr Med, Professor of Neurology, Director of Danish Headache Center

Medication overuse headache (MOH) presents a therapeutic challenge. It is relatively common, with an overall prevalence in the general population of 1–2% but up to 50% in specialised headache clinics, and the cost of management is three times greater than for migraine. It is associated with depression and anxiety, disability and impaired quality of life.[1] However, although this challenge is recognised there is uncertainty about the best management strategy.

There are three strategies to treat MOH: start prophylaxis after the overused medication has been withdrawn, while attempting withdrawal or without attempting withdrawal and waiting for the patient to stop overuse.[2-4]

The first strategy was evaluated in a randomised open-label trial in which 72 patients with MOH were randomised to 2 months' detoxification with either no analgesics or acute migraine-medication or restriction of acute medication to 2 days/week.[5] After 12 months, 74% of patients were continuing the medication withdrawal strategy compared with 46% with the restriction strategy. Mean monthly migraine days were reduced by 7.8 and 4.6 days respectively ($p<0.01$) and cure rates were not statistically different (89% vs 81% respectively). Patients' assessments of the feasibility of their management strategy significantly favoured complete withdrawal over restriction (Figure 1).[6]

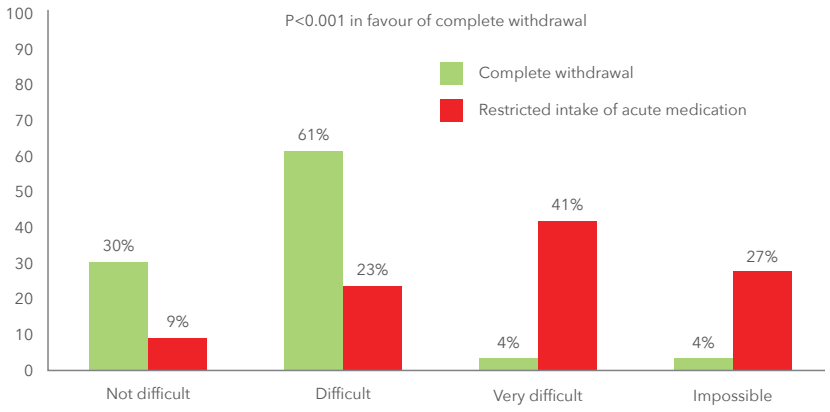

Figure 1 Feasibility of management strategy at 12-months follow-up.
Source: Engelstoft 2019, figure 2, p. 1167. Reproduced with permission of the European Pain Federation

The second strategy of initiating prophylaxis and withdrawing the overused medication at the same time: reduced medication use and pain intensity and duration; improved depression, anxiety and quality of life, and reduced healthcare costs; 78% of patients reverted to episodic headache and 83% were considered cured of MO.7 This was associated with a significant reduction in direct healthcare costs in all of the five countries participating in the study (Figure 2).[7,8]

To test the third strategy of prevention alone, the three strategies - withdrawal plus preventive treatment, preventive treatment without withdrawal, or withdrawal with optional preventive treatment 2 months after withdrawal - were compared in a randomised trial 102 patients with MOH.[9] After 6 months' follow up, withdrawal plus preventive treatment reduced monthly headache days the most (12.3 days vs 9.9 and 8.5 days respectively). This strategy was also associated with an 80% higher chance of reverting to episodic headache and a 30% higher chance of cure of MOH compared with prevention alone.

Uncertainty remains about some important outcomes, including the proportion of patients who revert to episodic headache or are cured of MOH; further, there has been little economic analysis of the cost effectiveness of these interventions. A recent review estimated that the number needed to treat (NNT) with anti-CGRP monoclonal antibodies is 3-8 for migraine prevention to

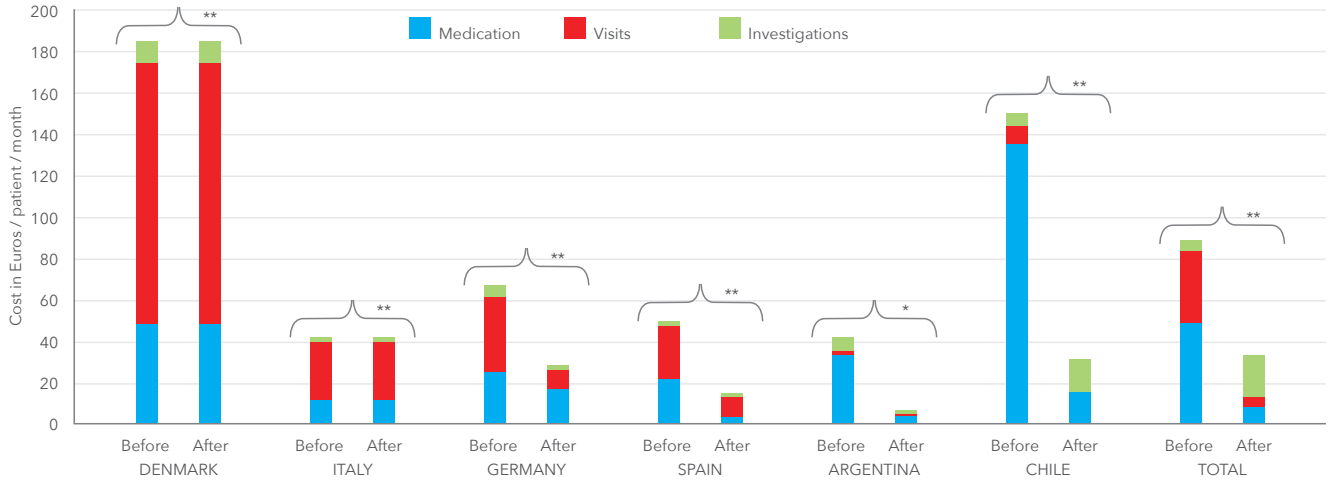

Figure 2 Distribution of decreased direct healthcare costs after treatment of medication-overuse headache (n=651). Source: Jellestad 2019. Reproduced with permission of SAGE

reduce attacks by at least 50%, with the number needed to harm (NNH) of >40. Older preventive therapies may be slightly more effective (NNT 2–4 for topiramate, valproate, beta blockers and candesartan) but they have a higher risk of adverse effects with NNHs of 2–17 for most and >20 for candesartan.[10] The NNT for preventing attacks with anti-CGRP monoclonal antibodies in patients with MOH is even lower (1.5–2.0) and, on the evidence so far, the NNH is no higher than in the migraine population as a whole. Overall, early detoxification is thus very effective and provides a higher cost–benefit than CGRP antibodies alone.

References

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396:1204-1222.
2. Evers S, Jensen R; European Federation of Neurological Societies. Treatment of medication overuse headache – guideline of the EFNS headache panel. Eur J Neurol. 2011;18:1115-21.
3. Diener HC, Dodick D, Evers S, et al. Pathophysiology, prevention, and treatment of medication overuse headache. Lancet Neurol. 2019;18:891-902.
4. Carlsen LN, Munksgaard SB, Nielsen M, et al. Comparison of 3 treatment strategies for medication overuse headache: a randomized clinical trial. JAMA Neurol. 2020;77:1069-1078.
5. Carlsen LN, Munksgaard SB, Jensen RH, et al. Complete detoxification is the most effective treatment of medication-overuse headache: a randomized controlled open-label trial. Cephalalgia. 2018;38:225-236.
6. Engelstoft IMS, Carlsen LN, Munksgaard SB, et al. Complete withdrawal is the most feasible treatment for medication-overuse headache: a randomized controlled open-label trial. Eur J Pain. 2019;23:1162-1170.
7. Tassorelli C, Jensen R, Allena M, De Icco R, Katsarava Z, Miguel Lainez J, Leston JA, Fadic R, Spadafora S, Pagani M, Nappi G; COMOESTAS Consortium. The added value of an electronic monitoring and alerting system in the management of medication-overuse headache: a controlled multicentre study. Cephalalgia. 2017;37:1115-1125.
8. Jellestad PL, Carlsen LN, Westergaard ML, et al; COMOESTAS Consortium. Economic benefits of treating medication-overuse headache - results from the multicenter COMOESTAS project. Cephalalgia. 2019;39:274-285.
9. Carlsen LN, Munksgaard SB, Nielsen M, et al. Comparison of 3 treatment strategies for medication overuse headache: a randomized clinical trial. JAMA Neurol. 2020;77:1069-1078.
10. Schoenen J, Manise M, Nonis R, et al. Monoclonal antibodies blocking CGRP transmission: an update on their added value in migraine prevention. Rev Neurol (Paris). 2020;176:788-803.

Cardiovascular diseases

Marja-Liisa Sumelahti,
MD, PhD, Specialist in Neurology, Faculty of Medicine and Health Technology, Tampere University, Finland

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an hereditary angiopathy caused by mutations in the NOTCH3 gene. It is rare, with a prevalence of 5 per 100,000; it is associated with an increased risk of transient ischaemic attack, cognitive defects and migraine developing after age 45, and has a highly variable progressive clinical course.

This case study describes a woman aged 47 in 2020 with CADASIL and cardiovascular risk factors (migraine, metabolic syndrome, mild depression, anxiety). At age 34, she had a child and experienced a brainstem aura. She was diagnosed with CADASIL in 2013, aged 39. Imaging demonstrated increasing brain white matter hyperintensity. She was prescribed aspirin, candesartan and atorvastatin.

CT scans in 2013 and 2017 showed bilateral and increased white matter lesion volume; MRI in 2013 showed bilateral periventricular white matter lesions with no contrast enhancement. An MRI in 2020 demonstrated a marginal increase in brain atrophy with increased supratentorially confluous and prominent white matter lesions temporomedially and focally in the thalamus.

This patient had frequent migraine attacks with and without aura leading to chronicification, medication overuse headache and menstrual migraine. The attacks had proved difficult to treat - triptans are contraindicated and prophylaxis had failed – and she was forced to take time off work. In 2019, she was experiencing 5–15 attacks per month. Lamotrigine 100 mg/day was prescribed; this was well tolerated and improved migraine with aura. Acetazolamide was added, with no tolerability issues. Because of her cardiovascular risk factors, onabotulinum toxin A was also tried. Treatment with erenumab 140 mg monthly was then initiated. This reduced migraine attacks and was well tolerated, resulting in an improvement in quality of life. Cognitive function is currently unaffected.

There are now several questions about the best way forward. Is there a case for suspending treatment with erenumab and replacing it with onabotulinum toxin A? Will the ditans and gepants offer any advantage over paracetamol and NSAIDs to treat acute attacks? How should cardiovascular risk be assessed and what should be the role of aspirin?

Comorbidity of migraine and epilepsy

Annelies Van Dycke,
MD, PhD Neurologist, AZ Sint-Jan, Bruges, Belgium

The prevalence of epilepsy is 0.5–1.0% and that of migraine is 15–18% in women, 6% in men and 4% in children. Epidemiological studies show that comorbidity between these disorders is high, with migraine occurring in about 25% of people with epilepsy and epilepsy reported in 1–2% of people with migraine.[1]

This case study describes Jana, who was born in 1994. She had no risk factors for epilepsy and there was no history of epilepsy in the family. Her father has migraine without aura, for which he takes preventive treatment with a beta blocker. Jana developed migraine without aura in 2015, experiencing about one attack per month. She experienced her first seizure on 1 October 2018 and on 4 October she had multiple seizures. All were preceded by severe migraine headache without aura. MRI and EEG were normal. She was prescribed levetiracetam 500 mg twice daily, increased to 1000 mg twice daily. Treatment was switched first to topiramate (due to intolerance of levetiracetam). Because of side effects on topiramate, lamotrigine was started (up to 150 mg twice daily) with complete seizure control. Episodic migraine has improved since starting preventive treatment with propranolol 80 mg/day.

Jana's case is an example of comorbidity between migraine and epilepsy. There is a temporal relationship between epileptic seizures and headache symptoms. Pre-ictal migraine may or may not be preceded by aura. Post-ictal migraine is the most common manifestation, with migraine or tension type headache reported by 37–51% of patients. Ictal migraine is rare.

Both migraine and epilepsy are associated with impaired quality of life and their comorbidity is under-recognised and under-treated. Topiramate or valproate are arguably the anti-epileptic drugs of choice due to their efficacy in migraine prevention but treatment of epilepsy with migraine has not been systematically studied (and valproate is not first choice in women of childbearing potential). Their concurrence is probably multifactorial in origin, with neuronal hyperexcitability, stimulation of the trigeminovascular system and genetic predisposition all potential contributory factors.

Reference

1. Haut SR, Bigal ME, Lipton RB. Chronic disorders with episodic manifestations: focus on epilepsy and migraine. Lancet Neurol. 2006;5:148-157.

Pregnancy and lactation

Anne Christine Poole,
General Practitioner and Headache Specialist, Oslo Headache Centre

This case study describes the challenges of counselling patients with migraine about the safety of treatment during pregnancy and while they are breast feeding.

Linda (aged 34) is married to Carl (43); they have a healthy 7-year-old child. Linda first developed migraine at age 13 and this became chronic in the last 10 years. During her pregnancy, migraine attacks became severe and were associated with vomiting, on one occasion resulting in hospital admission for intravenous rehydration. She now takes an anti-CGRP monoclonal antibody as preventive therapy and for the first time in her adult life she is doing well, working full time in a job she loves. Carl wants a large family; Linda, recalling the experience of her first pregnancy, is reluctant. They have come to the headache clinic for counselling.

Linda is not unique among women with migraine, 6% of whom say they are having fewer or no children because of their condition.[1] However, there may be many issues underlying her reluctance about another pregnancy in addition to her difficult symptoms, such as concern about caring for her children if she is ill, the risk of depression, lack of family support and the negative impact on her career.

Preconceptional guidance should include education about the effect of pregnancy on migraine. Treatment with an anti-CGRP monoclonal antibody should be discontinued four months before stopping contraception. An alternative preventive treatment should be offered and management of acute attacks should be tailored to each individual. The patient should be reassured that they will be helped and guided throughout their pregnancy, and given an appointment for a consultation after the birth.

The take-home message is that preconceptual guidance about migraine treatment is of great importance and should be offered to both partners. They should also be offered a scheduled meeting after the birth.

Reference

1. Steiner TJ, Stovner LJ, Katsarava Z, et al. The impact of headache in Europe: principal results of the Eurolight project. J Headache Pain. 2014;15:31. doi: 10.1186/1129-2377-15-31.

Pharmacology of monoclonal antibodies and gepants

Eili Tranheim Kase,
PhD, Associate Professor, Department of Pharmacy, University of Oslo

Anti-CGRP monoclonal antibodies probably cross the placenta but there is no evidence of harm in humans as a result; levels in breast milk are very low, especially after one week. There are no data on human exposure to gepants during pregnancy but animal studies at doses comparable with clinical doses suggest any risk is low.

There is little information about the safety of anti-CGRP monoclonal antibodies and gepants in the treatment and prevention of migraine in humans during pregnancy and lactation. However, experience with monoclonal antibodies in the treatment of inflammatory bowel and joint disorders during pregnancy has accumulated from many years of use. Based on these data, guidance on the use of monoclonal antibodies during pregnancy and lactation recommends prenatal counselling, stating there are no known contraindications to breastfeeding during treatment and that infants should be followed up, especially during the first 6 months.[1] A recent review of two monoclonal antibodies (ustekinumab and vedolizumab) and the small molecule tofacitinib concluded that the monoclonal antibodies are probably safe but expressed doubt about the safety of small molecules.[2] These findings are potentially relevant when considering the safety of anti-CGRP monoclonal antibodies and gepants, which are small molecules.

Evidence from animal studies on anti-CGRP monoclonal antibodies in pregnancy is reassuring.[3] Based on such data, Norwegian guidance on prescribing fremanezumab, galcanezumab and erenumab during pregnancy and while breastfeeding is cautious and their use is recommended if the anticipated benefit outweighs the possible risk (Table 1).

The anti-CGRP monoclonal antibodies are all subtypes of IgG, they have elimination half-lives of 27–30 days and all have a monthly dose regimen, but fremanezumab may also be administered quarterly. These dose regimens are associated with marked differences in plasma levels.[4] This figure shows that measurable plasma levels persist even 120 days after administration even after the lower dose; this should be borne in mind when counselling patients who are planning pregnancy.

Period	Evidence	Advice
Close to conception	Not studied	Avoid 4 months before planned pregnancy
First trimester	Not studied	No observed teratogenic effects
Second and third trimesters	Not studied	Theoretic risk of pre-eclampsia
Lactation	Not studied	Probably no transfer to breast milk one week after birth

Table 1. Advice on the use of anti-CGRP monoclonal antibodies during pregnancy and lactation (https://www.legeforeningen.no/foreningsledd/fagmed/norsk-gynekologisk-forening/veiledere/veileder-i-fodselshjelp/nevrologiske-sykdommer-i-svangerskapet)

The gepants are classical competitive antagonists at the CGRP receptor.[5] Ubrogepant has received regulatory approval in the United States to treat acute migraine; it is not yet licensed in Europe. Preclinically, high doses of ubrogepant were associated with increased foetal mortality in the rabbit and, at doses causing maternal toxicity during pregnancy and lactation, with underweight newborns in the rat. Doses consistent with the maximum human dose were not associated with toxicity. There are no data on its safety in humans during pregnancy or lactation.

Passive placental transfer is determined by molecular weight: in general, compounds with a molecular weight of <0.5 kDa diffuse into the placenta. The molecular weight of ubrogepant is 0.55 kDa; this is so close to the threshold that the possibility of transfer cannot be excluded. The anti-CGRP monoclonal antibodies have a molecular weight of approximately 150 kDa; passive transfer is therefore unlikely but they are actively transported into the placenta. However, there has been no evidence

to date that they are associated with teratogenicity in clinical use.[6,7] Information about the safety of migraine treatments in pregnancy and lactation could be improved by establishing an international registry to record exposures and long term follow up.

References

1. Pham-Huy A, Sadarangani M, Huang V, et al. From mother to baby: antenatal exposure to monoclonal antibody biologics. Expert Rev Clin Immunol. 2019;15:221-229.
2. Gisbert JP, Chaparro M. Safety of new biologics (vedolizumab and ustekinumab) and small molecules (tofacitinib) during pregnancy: a review. Drugs. 2020l;80:1085-1100.
3. Bussiere JL, Davies R, Dean C, et al. Nonclinical safety evaluation of erenumab, a CGRP receptor inhibitor for the prevention of migraine. Regul Toxicol Pharmacol. 2019;106:224-238.
4. Cohen-Barak O, Weiss S, Rasamoelisolo M, et al. A phase 1 study to assess the pharmacokinetics, safety, and tolerability of fremanezumab doses (225 mg, 675 mg and 900 mg) in Japanese and Caucasian healthy subjects. Cephalalgia. 2018;38:1960-1971.
5. Do TP, Guo S, Ashina M. Therapeutic novelties in migraine: new drugs, new hope? J Headache Pain. 2019;20:37. doi: 10.1186/s10194-019-0974-3.
6. de Vries T, Villalón CM, MaassenVanDenBrink A. Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans. Pharmacol Ther. 2020;211:107528. doi: 10.1016/j.pharmthera.2020.107528.
7. Palmeira P, Quinello C, Silveira-Lessa AL, et al. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012;2012:985646. doi: 10.1155/2012/985646.

Migraine management during pregnancy and breastfeeding

Mattias Linde,
MD, PhD, Professor of Neurology, Norwegian Advisory Unit for Headaches and NTNU Consultant Neurologist, Tjörn Headache Clinic

The group of people most highly burdened by migraine are women of childbearing age, with about 1 in 5 of 30- to 39-year-olds affected.[1] The challenge of treatment and prevention during pregnancy and while breast feeding is therefore a frequent one. Fortunately, the frequency of migraine attacks declines towards the time of delivery; however, there is often a marked increase during the puerperium.[2]

All the Scandinavian countries have developed guidelines on the treatment and prevention of migraine during pregnancy and the puerperium and their recommendations are consistent with one another. In addition, the European Headache Federation recently updated its guidance on management in primary care.[3] These recommendations are summarised in Table 1.

Paracetamol is safe for all indications but is often not effective in the puerperium. Efficacy may be improved in combination with codeine but opioids should be avoided in the third trimester and the early weeks of lactation because they cause sedation in the newborn. Sumatriptan is the only triptan for which there is evidence of safety, though this comes largely from spontaneous reports. It is lipophilic but is safe during lactation as long as feeding is delayed for 12 hours after the dose (the interval for eletriptan is 24 hours due to its longer half-life), or milk is expressed before the dose. Exercise (aerobic physical activity) is as effective as topiramate in preventing migraine[4] and migraine severity is inversely correlated with level of activity.[5] Exercise should therefore be recommended for pregnant women as long as they are able to carry it out, though it is not practicable during the puerperium. Most countries state that valproate is absolutely contraindicated in all women; it is included in the Denmark guideline as an option but it is rarely prescribed.

References

1. Linde M, Stovner LJ, Zwart JA, et al. Time trends in the prevalence of headache disorders. The Nord-Trondelag Health Studies (HUNT 2 and HUNT 3). Cephalalgia. 2011;31:585-96.
2. Kvisvik EV, Stovner LJ, Helde G, et al. Headache and migraine during pregnancy and puerperium: the MIGRA-study. J Headache Pain. 2011;12:443-51.
3. Steiner TJ, Jensen R, Katsarava Z, et al. Aids to management of headache disorders in primary care (2nd edition): on behalf of the European Headache Federation and Lifting The Burden: the Global Campaign against Headache. J Headache Pain. 2019;20:57. doi: 10.1186/s10194-018-0899-2.
4. Varkey E, Cider A, Carlsson J, et al. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. Cephalalgia. 2011;31:1428-38.
5. Varkey E, Hagen K, Zwart JA, et al. Physical activity and headache: results from the Nord-Trøndelag Health Study (HUNT). Cephalalgia. 2008;28:1292-7.

	Acute treatment	Prophylaxis
Pregnancy	1. Paracetamol - lowest possible dose 2. If necessary, metoclopramide (only trimesters 1 and 2) 3. COX-inhibitors (only trimester 2) 4. Paracetamol + codeine (caution in trimester 3) 5. Sumatriptan subcutaneously (limited safety data)	1. Exercise 2. Metoprolol or propranolol (low dose, only trimesters 1 and 2) 3. Amitriptyline (low dose, only trimesters 1 and 2) 4. Onabotulinum toxin A (chronic migraine only, PREEMPT-protocol) 5. Anti-CGRP monoclonal antibodies should be avoided 6. Candesartan, topiramate, CGRP-mAbs contraindicated 7. Valproate absolutely contraindicated
Lactation	1. Paracetamol is safe 2. Ibuprofen first choice among NSAID 3. Sumatriptan OK but avoid breastfeeding next 12 hrs 4. Eletriptan OK but avoid breastfeeding next 24 hrs 5. Paracetamol + codeine last option – avoid first weeks	1. Non-pharmacological prophylaxis 2. Metoprolol or propranolol 3. Amitriptyline 4. Valproate (option in Denmark) 5. Onabotulinum toxin A not proven safe therefore not recommended

Table 1. Summary of guidelines on the management of migraine during pregnancy and lactation[3]

Current preventative migraine treatments and the risk of infections

Marja-Liisa Sumelahti,
MD, PhD, Specialist in Neurology, Faculty of Medicine and Health Technology, Tampere University, Finland

There has been concern during the Covid pandemic that the immunosuppressive effects of medicines may increase the risk of infection. Little is known about the effect of migraine preventive medication on immune function but laboratory evidence of immunosuppression has not been reflected in clinical practice. Despite theoretical concerns, CGRP antagonists may confer some degree of protection against the complications of Covid.

The migraine population is a diverse group with different risk profiles for inflammatory and immune responses. In Finland, 83% of people experiencing at least 4 monthly migraine days take prophylaxis, most commonly a beta-blocker (43%) but also anti-epileptic drugs (35%), antidepressants (20%) and onabotulinum toxin A (15%).[1] These agents also have other indications and it is therefore possible that people with migraine are exposed to multiple risks from comorbidity, drug interactions and adverse effects. In the Covid era, it is therefore important to consider whether migraine treatments are associated with an increased risk or reduced tolerance of infection.

Some anti-epileptic drugs have been shown to reduce the production of cytokines and exert anti-inflammatory activity in vitro – for example, topiramate reduces production of tumour necrosis factor, which in theory may increase the risk of opportunistic infection.[2] However, a meta-analysis of randomized, double-blind, placebo-controlled trials investigating any anti-epileptic drug for any indication concluded that the risk of infection was significantly but only slightly increased overall (by 1%), though by somewhat more by topiramate (4%) and brivaracetam and levetiracetam (3%).[2]

Data on other migraine preventive treatments are sparse. A retrospective cohort study compared outcomes in patients prescribed or not prescribed a beta-blocker after stroke.[3] Beta-blockers did not reduce the incidence of pneumonia but were associated with a 35% lower risk of urinary tract infection. The reasons for this difference were unknown. The immunomodulatory effects of antidepressants may contribute to their therapeutic activity: a response to treatment is associated with a reduction in levels of several proinflammatory cytokines, including the interleukins IL-1, IL-6, IL-7, IL-8 and IL-10, and granulocyte colony-stimulating factor and interferon-γ.[4] Whether this affects the risk of infection is not known. A prospective observational study of 633 patients with chronic migraine treated with onabotulinum toxin A reported no infections.[5]

It was recognised early in the course of the pandemic that the SARS-CoV-2 virus binds to angiotensin-converting enzyme 2 receptors on endothelial and smooth muscle cells.[6] Angiotensin 2 is a pro-inflammatory vasoconstrictor, that contributes to organ damage in sites with high receptor expression such as the lung, heart, brain and small intestine. The angiotensin receptor blocker candesartan may help to stabilise endothelial function in patients with Covid. The anti-inflammatory effects of angiotensin receptor blockers include reduced oxidative stress and reversing endothelial dysfunction by mechanisms that are unrelated to their blood pressure lowering effects. With no evidence of harm and the possibility of benefit, the American College of Cardiology, the American Heart Association and the Heart Failure Society of America have recommended continuing treatment with candesartan during the pandemic.[7]

CGRP is a vasodilator that promotes angiogenesis and has immunomodulatory activity. Theoretically, blocking its effects could be deleterious.[8,9] However, CGRP release is increased by viral infection and acute lung injury; it contributes to the acute and chronic lung injury that activates acute respiratory distress syndrome and affects the immune response by modulating the release of cytokines and interleukins. In light of this, the United States Food and Drug Administration has approved a trial of the CGRP antagonist vazegepant to determine its value as a treatment for the pulmonary complications of Covid.[10]

In summary, anti-CGRP monoclonal antibodies have no known immunosuppressive effects and no

known targets in the immune system. Because they are highly specific for CGRP, they are unlikely to be associated with off-target effects.[11-13]

References

1. Sumelahti ML, Sumanen M, Sumanen MS, et al. My Migraine Voice survey: disease impact on healthcare resource utilization, personal and working life in Finland. J Headache Pain. 2020;21:118. doi: 10.1186/s10194-020-01185-4.
2. Zaccara G, Giovannelli F, Giorgi FS, et al. Do antiepileptic drugs increase the risk of infectious diseases? A meta-analysis of placebo-controlled studies. Br J Clin Pharmacol. 2017;83:1873-1879.
3. Maier IL, Karch A, Mikolajczyk R, et al. Effect of beta-blocker therapy on the risk of infections and death after acute stroke--a historical cohort study. PLoS One. 2015 Feb 2;10(2):e0116836. doi: 10.1371/journal.pone.0116836.
4. Szałach ŁP, Lisowska KA, Cubała WJ. The influence of antidepressants on the immune system. Arch Immunol Ther Exp (Warsz). 2019;67:143-151.
5. Ahmed F, Gaul C, García-Moncó JC, et al; REPOSE Principal Investigators. An open-label prospective study of the real-life use of onabotulinumtoxinA for the treatment of chronic migraine: the REPOSE study. J Headache Pain. 2019;20:26. doi: 10.1186/s10194-019-0976-1.
6. Hess DC, Eldahshan W, Rutkowski E. COVID-19-related stroke. Transl Stroke Res. 2020;11:322-325.
7. American College of Cardiology, American Heart Association, Heart Failure Society of America. HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19, https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19; accessed December 2020.
8. Skaria T, Mitchell KJ, Vogel O, et al. Blood pressure normalization-independent cardioprotective effects of endogenous, physical activity-induced αCGRP (α Calcitonin Gene-Related Peptide) in chronically hypertensive mice. Circ Res. 2019;125:1124-1140.
9. Mulder IA, Li M, de Vries T, et al. Anti-migraine calcitonin gene-related peptide receptor antagonists worsen cerebral ischemic outcome in mice. Ann Neurol. 2020;88:771-784.
10. Biohaven Pharmaceuticals. Biohaven Receives FDA May Proceed Letter to Begin Phase 2 Trial of Intranasal Vazegepant to Treat Lung Inflammation After COVID-19 Infection. 9 April 2020. https://www.biohavenpharma.com/investors/news-events/press-releases/04-09-2020.; accessed December 2020.
11. Han L, Liu Y, Xiong H, et al. CGRP monoclonal antibody for preventive treatment of chronic migraine: an update of meta-analysis. Brain Behav. 2019;9:e01215. doi: 10.1002/brb3.1215.
12. Dodick DW. CGRP ligand and receptor monoclonal antibodies for migraine prevention: Evidence review and clinical implications. Cephalalgia. 2019;39:445-458.
13. Levin M, Silberstein SD, Gilbert R, et al. Basic considerations for the use of monoclonal antibodies in migraine. Headache. 2018;58:1689-1696.

Follow-up of migraine treatment in the days of pandemic outbreak - is telehealth the answer?

Gürdal Sahin,
MD, PhD, Specialist in Neurology and Head of the Skåneuro Private Headache and Movement Disorders Clinic, Institution for Clinical Sciences, Lund University

Social distancing during the Covid pandemic has limited clinicians' ability to provide face-to-face care and disrupted the assessment, monitoring and supervision normally provided in outpatient clinics. Telemedicine is an option for providing care remotely that offers service continuity, with some success in the management of headache.[1-3] Its uptake during the pandemic may foretell a wider role in the future (Figure 1).

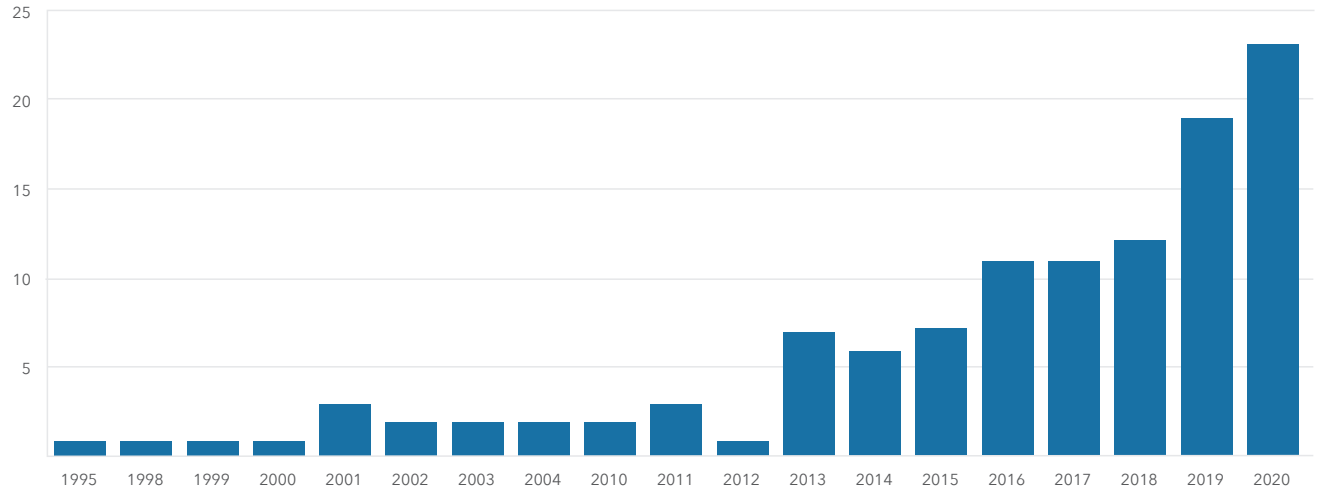

Figure 1 Number of publications using video-based telemedicine

Telemedicine offers several advantages. Patients have access to specialists and options for on-demand consultation. Transportation is unnecessary and there are no travel costs. Patients don't need to take time off work and arranging care for children and older people is unnecessary. No time is wasted in the waiting room and – particularly relevant at the moment – there is no risk of picking up an infection from other patients. The downside is that the clinicians are limited in what they can do: it is harder to comfort patients, difficult to carry out examinations and to have a team visit, and impossible to administer injections. Technology also presents challenges, such as equipment failure, dropped calls and slow internet connections, and the need to ensure privacy.

The reality of a digital consultation usually fails to match the aspiration. Ideally, the clinician would be able to talk to the patient while having immediate access to notes, imaging studies and the advice of colleagues (Figure 2a). The real digital consultation is typically more limited (Figure 2b) but at the minimum requires two computer monitors and a dedicated online patient portal.

A digital consultation should be conducted as if it was an in-person visit. Patients should be given instructions in advance on how to prepare for it; it should be carried out in a quiet environment and a professional setting (e.g. the clinician should not wear casual clothes). The consultation should be documented and delivered using a platform compliant with General Data Protection Regulation (GDPR) requirements. Facetime and Skype are not suitable. The American Academy of Neurology has produced a video providing guidance on conducting a neurological examination via telemedicine (https://youtu.be/KGlFCWWZGCY).

Events that are difficult to manage remotely require alternative strategies. For example, the antipsychotic ziprasidone is effective in refractory

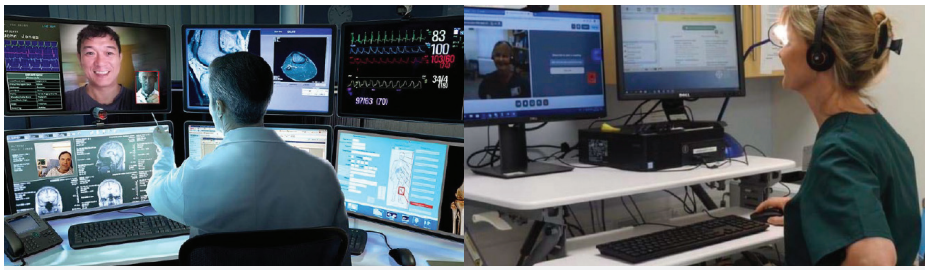

Figure 2 (a) The ideal digital consultation and (b) reality

First-time thunderclap headache
Headache and fever with altered mental status
New-onset neurologic deficits
Vision loss
Medication side effects
Possible cerebrospinal fluid leak
Screen all patients reporting new-onset headache or worsening of an existing headache disorder for COVID-19

Table 1. Red flag signs and symptoms indicating that a face-to-face consultation is essential

status migrainosus and can be given orally or by intramuscular injection;[4] migraine prevention with an anti-CGRP monoclonal antibody can be started with an autoinjector;[5] and wearing off of onabotulinum toxin A can be managed by increasing the dose of preventive therapy or substituting an oral alternative.[6] It is important to remember lifestyle modification and to optimise exercise, diet and stress management; a patient diary can have added value. Red flag symptoms indicating that a face-to-face consultation is needed are listed in Table 1.

Payment systems have been slow to catch up with this change in the way healthcare is delivered. Reimbursement is often partial and essential components such as phone calls, emails and online education are unpaid or less compensated. However, digital appointments usually take up as much clinician time as the face-to-face equivalent.

In summary, the response of healthcare services to the Covid pandemic has been to redeploy resources to frontline care and provide many outpatient services remotely. Migraine care should be delivered proactively; safe and effective measures for remote care are available. However, technology needs improvement if we are going to maximise the potential of telemedicine.

References

1. Friedman DI, Rajan B, Seidmann A. A randomized trial of telemedicine for migraine management. Cephalalgia. 2019;39:1577-1585.
2. Müller KI, Alstadhaug KB, Bekkelund SI. Acceptability, feasibility, and cost of telemedicine for nonacute headaches: a randomized study comparing video and traditional consultations. J Med Internet Res. 2016;18:e140. doi: 10.2196/jmir.5221.
3. Müller KI, Alstadhaug KB, Bekkelund SI. Telemedicine in the management of non-acute headaches: a prospective, open-labelled non-inferiority, randomised clinical trial. Cephalalgia. 2017;37:855-863.
4. Landsness EC, Wang LH, Bucelli RC. Ziprasidone as a potential abortive therapy for status migrainosus. Neurohospitalist. 2016;6:151-156.
5. Dodick DW. CGRP ligand and receptor monoclonal antibodies for migraine prevention: evidence review and clinical implications. Cephalalgia. 2019;39:445-458.
6. Robblee J, Starling AJ, Halker Singh RB et al. Teleneurology for primary headache disorders. Practical Neurology 2020;June:31-9.

Sweden, Denmark, Norway and Finland have independently developed their regulations for reimbursing treatment with anti-CGRP monoclonal antibodies, resulting in different levels of access to treatment and inconsistent eligibility criteria.

Sweden

Ingela Nilsson Remahl
MD, PhD, Head of the Headache Center, Karolinska University Hospital

An anti-CGRP monoclonal antibody may be prescribed for patients with chronic migraine for whom at least two preventive treatments have proved unsuccessful. Patients must keep a migraine diary for the 2–3 months preceding and following initiation using the Swedish Headache Register. Treatment may only be prescribed by a neurologist or physician working at a headache clinic who has experience of treating patients with severe migraine. Treatment must be evaluated after three months and continued only when a ≥30% reduction in migraine days has been achieved. It should then be re-evaluated every 12–18 months. Galcanezumab is recommended as the agent of first choice (at the time of this presentation, 28 November 2020).

In Sweden, all residents have a right to treatment regardless of where they live, their income or their social status but how this obligation is implemented varies between the six health care regions and 21 councils, and also between hospitals. Patients pay the first 2,350 SEK per year of medicines costs, after which they receive full reimbursement. The Swedish Headache Society is currently developing uniform treatment criteria to ensure equal access across Sweden.

Denmark

Lars Bendtsen
MD, PhD, Associate Professor, Danish Headache Center, Department of Neurology, Rigshospitalet, Glostrup, University of Copenhagen, Denmark

In Denmark, anti-CGRP monoclonal antibodies can only be prescribed by neurologists working in a Danish hospital (not private practice). Treatment is free for patients and costs are met by the hospital.

Anti-CGRP monoclonal antibodies are prescribed according to national guidelines developed by the Medicinrådet. Eligible patients have chronic migraine that has not responded to treatment with at least one antihypertensive agent and at least one anti-epileptic drug. Medication overuse must be treated before starting therapy and treatment with onabotulinum toxin A must be stopped. The least expensive anti-CGRP monoclonal antibody is the agent of choice unless there are strong reasons for prescribing an alternative. Patients must be closely followed up and headache days, headache severity and use of acute medications must be documented. Treatment must be reviewed after three months and continued only if moderate/severe headache days have been reduced by ≥30%. Effectiveness and adverse effects should be reviewed every three months. Treatment should be paused after one year to determine whether it is still necessary.

Norway

Lars Jacob Stovner
MD, PhD, Professor of Neurology, Norwegian University of Science and Technology and Norwegian Advisory Unit on Headaches, St. Olavs Hospital, Trondheim, Norway

The Norwegian Health Economic Administration (HELFO) administers the 'Blue Prescription' national insurance scheme under which the costs of medicines are reimbursed. Unlike other migraine treatments, anti-CGRP monoclonal antibodies are not covered by this scheme. Instead, their cost is reimbursed on individual application which must be renewed annually. The application can be made by a neurologist or a doctor working at the neurology department, or a doctor in a private hospital employing at least one neurologist. Treatment of patients aged under 18 is an unlicensed use but the same doctors and also a pediatrician are eligible to make the application.

Eligible patients have chronic migraine according to ICHD-3 criteria. The application must document migraine severity (monthly migraine headache days), previous preventive therapy, evidence of medication overuse headache and state that discontinuation of acute treatments has been attempted. Previous treatment with one of at least three pharmacological classes must have been unsuccessful. This may have been due to lack of effectiveness or adverse effects but contraindication is not considered a valid reason for not attempting treatment. For patients who have chronic migraine despite treatment with onabotulinum toxin A and who wish to start with an anti-CGRP monoclonal antibody it is recommended that this is done at least 4 months after the last injection, but if an increase in migraine cannot be tolerated, it can also be done immediately. Either way, if CGRP antibodies seem to work, one should try to discontinue onabotulinum toxin A, but in some cases both medicines may be necessary.

The patient must keep a headache diary. Treatment should be reviewed after 3 months and continued only if headache days (severity 2–3 on a scale of 0–4) were reduced by ≥30% during the previous 4 weeks. Clinicians are allowed discretion when interpreting the effectiveness criteria – for example, effectiveness may mean the patient manages with less acute medication, migraine relief has improved or the patient can be more active.

Finland

Marja-Liisa Sumelahti
MD, PhD, Specialist in Neurology, Faculty of Medicine and Health Technology, Tampere University, Finland

The Finland national health insurance scheme (KELA) reimburses patients at 40% of the cost of erenumab, fremanezumab and galcanezumab. Eligibility is determined by statements from a neurologist (the first and the second statement) or a physician having experience in migraine treatment (the third statement). Eligible patients must have at least 8 migraine days a month on average during a 3-month period with at least two preventive medications proving unsuccessful due to lack of effectiveness or they are not tolerated or they are contraindicated.

The statement procedure has two steps. After the first statement, the patient must achieve a ≥50% reduction in monthly migraine days over a 12-week period during the first 6 months. The response has to be evaluated at weeks 9-12. The second statement has to be submitted if the response is achieved and then the reimbursement will be continued for a further 2 years. A third statement is then granted if the improvement in monthly migraine days was sustained for the 2-year period. The first two statements must be made by a neurologist but any physician can make the third statement.

Nordic Migraine Symposium 20

Kinoveien 3A,
1337 Sandvika,
Norway

Teva Norway AS/03.2021