Editorials

Monoclonal antibodies for migraine prevention:

hope, hype, and health economy challenge

The annual prevalence of migraine in the UK is 7.6% in males and 18.3% in females.[1] Migraine is ranked globally as the second most disabling disease,[2] and is the second most frequent cause of short-term absence for non-manual employees with a cost of 2.25 billion GBP per year in the UK.[1] Over 30% of people with migraine have ≥4 attacks a month, of whom a quarter will have chronic migraine — arbitrarily defined as headache on ≥15 days of the month, of which eight are migraine.[3] Chronic migraine has a high impact and is associated with medication overuse headache and deteriorating psychosocial functioning.[3]

LIMITED CURRENT OPTIONS

Migraine is a complex biopsychosocial disease, and although lifestyle and psychological interventions complement drug treatment, evidence-based interventions for prevention are limited. All preventative drugs have been discovered by chance, and of the wide array of drugs used in practice only beta-blockers, amitriptyline, and topiramate in addition to botulinum toxin for chronic migraine reach the level of evidence required by the National Institute for Health and Care Excellence (NICE).[4] Seventy per cent of migraineurs will stop their oral preventers after a year,[1–3] the majority due to side effects or lack of effectiveness,[5] and there is a population of migraine sufferers that are refractory to all forms of treatment.

Since the triptans were introduced for acute treatment in 1991 the race has been on to develop a targeted approach to migraine prevention. One molecule has made it to the finishing line, calcitonin gene-related peptide (CGRP), a widely distributed neurotransmitter involved in vascular homeostasis and nociception.[6] CGRP is raised during a migraine attack, although its contribution to migraine pathophysiology is not clearly understood. Three self-administered subcutaneous monoclonal antibodies (MABs) are currently licensed in the UK, targeted either against CGRP or its receptor (see Table 1).

> *"... these drugs* [calcitonin gene-related peptide] *undoubtedly offer a significant breakthrough in the management of migraine ... But the reality may be more measured* [in terms of benefit]*."*

CAUTIOUS OPTIMISM

Described as 'game changers', 'life changing', and 'the end of a long drought', these drugs undoubtedly offer a significant breakthrough in the management of migraine where evidence-based preventive options are limited. But the reality may be more measured.

Benefit may be more modest than the hype suggests — outcomes are similar to current best practice.[7] However, they may offer advantages where current therapy has failed and work in the presence of medication overuse headache, which can limit the action of existing preventers. Onset of action is more rapid than existing therapy, which requires 8 weeks to judge effective benefit.

Side effect profiles are similar to placebo, but there are theoretical concerns in the longer term due to their vasoconstrictive properties.[8]

Table 1. Current status of licensed calcitonin gene-related peptide drugs in the UK

Drug	Dose	Status
Erenumab (Aimovig®)	70–140 mg monthly	Submitted and rejected by the National Institute for Health and Care Excellence (NICE) on the grounds of cost effectiveness. Accepted by the Scottish Medicines Consortium for chronic migraine, in whom three agents have failed
Fremanezumab (Ajovy®)	225 mg monthly or 675 mg 3-monthly	Accepted by the Scottish Medicines Consortium and NICE for chronic migraine, in whom three agents have failed
Galcanezumab (Emgality®)	120–240 mg monthly	Awaiting NICE submission

ECONOMIC CHALLENGES

The major challenge is to the health economy. MABs are expensive to develop and produce. Fremanezumab has been accepted by NICE for use in chronic migraine in England and Wales when three preventive medications have failed. The cost is 5400 GBP a year.[9]

This is the first time that a high-cost drug has been directed at a problematic and frequent disease, and highlights a number of issues from an economic perspective. First, the limitations of long-term economic modelling using short-term data in a condition where the natural history is not understood have been exposed with a very wide range of cost-effectiveness estimates. Second, a divergence of opinion on cost effectiveness between Scotland and England reflects not only the difficulties in economic modelling, but has led to an unacceptable situation of unequal access across the UK. Third, it highlights the importance of affordability rather than cost effectiveness, and the unreasonable expectations of pharmaceutical companies about what the NHS can afford.

WHAT CAN WE TELL OUR PATIENTS?

Other CGRP-directed therapies are being developed and future costs will inevitably be reduced, but where does this leave the GP when patients request this drug? They are certainly not a magic bullet — expert clinical opinion suggests that one-third of patients will have a significant improvement, one-third will have some improvement, and one-third will have no benefit. We can be cautiously optimistic that these agents will become available over the next year but only for those with severe disease impact, in whom current therapy has failed. However, the limited number of headache specialists in the NHS will inevitably cause delays in appropriate management.

In the meanwhile, it should be recognised

"This is the first time that a high-cost drug has been directed at a problematic and frequent disease, and highlights a number of issues from an economic perspective."

that the standard of migraine management in primary care is poor and the current focus should be on the diagnosis and appropriate management of migraine using current therapeutic options and relevant lifestyle interventions. If migraine is diagnosed early and managed effectively, then it is possible that the disease will not progress to frequent episodic or chronic migraine, which causes so much unmet need and becomes more resistant to treatment.

David Kernick,
GP, Exeter Headache Clinic, St Thomas's Health Centre, Exeter, UK.

Provenance
Freely submitted; externally peer reviewed.

Competing interests
David Kernick has received advisory income from Novartis, Teva, and Lilly; manufacturers of migraine preventer monoclonal antibodies.

DOI: https://doi.org/10.3399/bjgp20X711833

ADDRESS FOR CORRESPONDENCE

David Kernick
Exeter Headache Clinic, St Thomas's Health Centre, Exeter EX4 1HJ, UK.

Email: David.kernick@nhs.net

REFERENCES

1. Steiner TJ, Scher AI, Stewart WF. *et al.* The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. *Cephalalgia* 2003; **23(7):** 519–527.
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):** 1211–1259.
3. Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. *Curr Pain Headache Rep* 2011; **15(1):** 70–78.
4. National Institute for Health and Care Excellence. *Headaches in over 12s: diagnosis and management. CG150.* 2015. https://www.nice.org.uk/guidance/cg150 (accessed 1 Jun 2020).
5. Hepp Z, Bloudek LM, Varon SF. Systematic review of migraine prophylaxis adherence and persistence. *J Manag Care Pharm* 2014; **20(1):** 22–33.
6. Edvinsson L. CGRP receptor antagonists and antibodies against CGRP and its receptor in migraine treatment. *Br J Clin Pharmacol* 2015; **80(2):** 193–199.
7. Deen M, Correnti E, Kamm K, *et al.* European Headache Federation School of Advanced Studies (EHF-SAS). Blocking CGRP in migraine patients — a review of pros and cons. *J Headache Pain* 2017; **18(1):** 96.
8. Schuster NM, Rapoport AM. Calcitonin gene-related peptide targeted therapies for migraine and cluster headache: a review. *Clin Neuropharmacol* 2017; **40(4):** 169–174.
9. The National Institute of Health and Care Excellence. *Fremanezumab for preventing migraine. ID1368.* 2020. https://www.nice.org.uk/guidance/indevelopment/gid-ta10339 (accessed 2 Jun 2020).