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The most important advances in headache research in 2018

In 2018, many advances were made in headache research. In my view, one of the major advances was the publication of the third edition of the The International Classification of Headache Disorders (ICHD-3), which includes new diagnostic criteria for migraine with aura that better distinguish it from transient ischaemic attacks.[1] These criteria were previously in the appendix of the ICHD-2 and have now been included in ICHD-3. Patients with aura should now report at least three of the following six characteristics: 1) at least one aura symptom spreads gradually over at least 5 min; 2) two or more aura symptoms occur in succession; 3) each individual aura symptom lasts 5–60 min; 4) at least one aura symptom is unilateral; 5) at least one aura symptom is positive; 6) the aura is accompanied, or followed within 60 min, by headache. The classification of trigeminal neuralgia has also changed: trigeminal neuralgia is now subdivided into classical trigeminal neuralgia (neurovascular compression with morphological changes in the trigeminal root shown by MRI or during surgery) and idiopathic trigeminal neuralgia (no abnormalities by electrophysiological tests or MRI) on the basis of presence of degree of neurovascular contact; trigger factors are now required to establish a diagnosis; the absence of sensory abnormalities is no longer required for diagnosis; and the diagnosis of secondary trigeminal neuralgia (caused by an underlying disease) is now accepted.

Development and introduction of monoclonal antibodies against calcitonin gene-related peptide (CALCA; also known as CGRP) or the CGRP receptor are the most important advances in migraine therapy in decades. Three double-blind, randomised, placebo-controlled phase 3 trials[2-4] reported on the safety and efficacy of this new drug class. One trial assessed 875 patients with episodic migraine who received subcutaneous fremanezumab monthly (225 mg) or quarterly (675 mg), or placebo.[2] The study excluded patients who had previous treatment failure with two classes of anti-migraine medications. Compared with placebo, fremanezumab significantly reduced the mean number of migraine days over 12 weeks by 1·5 days (95% CI 0·93–2·01) with the monthly regimen and 1·3 days (0·72–1·79) with the quarterly regimen.[2] In the EVOLVE-1 trial,[3] 858 patients with episodic migraine received subcutaneous galcanezumab (120 mg or 240 mg) or placebo once per month for 6 months. Both galcanezumab doses significantly reduced monthly migraine days compared with placebo

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(reduced by 1·9 days [95% CI 1·4–2·5] for 120 mg and 1·8 days [1·2–2·3] for 240 mg). In the LIBERTY trial,[4] 246 patients with episodic migraine who previously did not respond to or tolerate 2–4 previous antimigraine treatments received subcutaneous erenumab (140 mg) or placebo every 4 weeks for 12 weeks. At week 12, 36 (30%) of 121 patients who received erenumab had a 50% or greater reduction from baseline in the mean number of monthly migraine days, compared with 17 (14%) of 125 in the placebo group (odds ratio 2·7 [95% CI 1·4–5·2]). Safety and tolerability profiles of erenumab, fremanezumab, and galcanezumab were similar to that of placebo.

Based on the positive safety, tolerability, and efficacy profiles of these monoclonal antibodies targeting either CGRP (fremanezumab and galcanezumab) or its receptor (erenumab), they have received their first marketing approvals for the preventive treatment of migraine in adults by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Specifically, the FDA and EMA approved erenumab subcutaneous injection with 70 and 140 mg monthly dosing options; the FDA approved fremanezumab subcutaneous injection with 225 mg monthly and 675 mg quarterly dosing options; and the FDA approved galcanezumab with a 120 mg monthly dosing option. With the approvals of these drugs, a specific and tolerable preventive treatment option can now be offered to patients with migraine.

Patients with migraine with aura often report an overlap between aura and headache and some patients report headache that occurs 20–30 min after onset of aura symptoms.[2] The electrophysiological phenomenon of cortical spreading depression, an intense neuronal and glial depolarisation wave that slowly propagates in grey matter, is the underlying mechanism of migraine with aura.[5] However, the mechanism by which cortical spreading depression activates pain-sensitive fibres outside of the blood–brain barrier, and thereby migraine headache, is not fully understood. Whether cortical spreading depression activates immune cells inside the blood–brain barrier (in the pia), outside the blood–brain barrier (in the dura), or in both was investigated in mice.[5] Using in vivo two-photon microscopy through the skull of mice, immune cells in the pia, subarachnoid space, and dura were tracked before and after occurrence of cortical spreading depression. By showing that cortical spreading depression activates pial macrophages within seconds, pial and dural dendritic cells within 5–8 min, and dural macrophages within 20 min, this study might explain how cortical spreading depression that occurs in the cortex (inside the blood–brain barrier) activates pain fibres in the dura (outside the blood–brain barrier). These translational data also suggested that activation of pial macrophages might explain cases in which aura and migraine begin simultaneously and that activation of dural macrophages might explain cases in which headache begins 20–30 min after aura.

In the years ahead, it will be important to establish predictive markers to identify responders and non-responders to monoclonal antibodies and thus individualise migraine prevention. Therefore, investigations of novel mechanisms (eg, drugs interacting with pituitary adenylate cyclase-activating polypeptide signalling) are needed. Cluster headache is one of the most painful types of headache and specific preventive therapies are needed. Studies investigating monoclonal antibodies targeting CGRP in patients with cluster headache are underway (NCT02397473 and NCT02397473). In 2019, the efficacy of anti-CGRP antibodies should be established, and hopefully those findings will represent a breakthrough in cluster headache treatment.

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I have received personal fees from Alder BioPharmaceuticals, Allergan, Amgen, Alder, Eli Lilly, Novartis, and Teva. I participated in clinical trials as the principal investigator for Alder, Amgen, OLE, GM-11 gamma-Core-R trials, Novartis, Amgen, and Teva. I serve as an associated editor of Cephalalgia, coeditor of the Journal of Headache and Pain, and I am President-elect of the International Headache Society and General Secretary of the European Headache Federation.

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