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New and Emerging Treatments for Migraine

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Abstract

Migraine can be extremely disabling with a considerable impact on the life of an individual in their ability to work or perform activities of daily living. The arrival of 'triptans' in the early 1990s saw a major change in the way migraines were treated, and 'triptans' remain the gold standard in treating an acute attack. For a long time there was very little progress in identifying new targets for acute treatment and there was virtually nothing new in migraine prevention. However, in recent times, considerable research has been made in understanding the pathophysiology of migraine and the coming decade should see a drastic change in treating and preventing migraines with potential neuro-pharmacological agents and non-invasive neuro-stimulation. This article briefly discusses the pathophysiology of migraine and reviews new therapeutic options as well as some promising treatments undergoing clinical trials.

Keywords: Migraine; Triptans; Cerebrovascular Disease; Onabotulinumtoxina

Introduction

Migraine has a lifetime prevalence of around 15% of the population with women (18%) affected more than men (8%) [1]. Recently, migraine has been identified as the 7th disabler [2]. The disorder, commonly seen in the productive life of an individual, has a significant impact on the ability to work or carry out activities of daily living. 75% of patients cannot function during an attack and around half require help from others [3]. In addition to direct healthcare costs, the disorder results in loss of 20 million working days a year as an indirect impact on the economy [1]. The occurrence of frequent attacks, inadequate pain relief to current therapies, adverse events and resistance to treatment emphasize the need for novel therapies for this disabling disorder. The discovery of 'triptans' in the early 90's saw a significant progress in treating acute attacks but not everyone benefits from it and there are restrictions to its use in patients with ischaemic cardiac and cerebrovascular disease. The approach to preventive treatment remained the use of established agents such as beta-blockers, tricyclic antidepressants and some anticonvulsants e.g. sodium valproate. Topiramate was a valuable addition although tolerability, cognitive side effects and teratogenicity limited its use.

Several theories on the pathophysiology of migraine exist, with no clear consensus on its cause or mechanism. The 'Holy Grail' of migraine therapy, therefore, has remained elusive. Recently, both invasive and non-invasive methods are emerging as promising therapeutic options, with renewed hope that migraineurs will benefit from better quality of life. The use of OnabotulinumtoxinA (Botox®), injection of steroid and local anaesthetic in the greater occipital nerve (greater occipital nerve blocks) and availability of some non-invasive neurostimulation devices (e.g. transcranial magnetic stimulation and Cefaly®) have added new dimensions to therapy. There are other neurostimulation devices undergoing trial. Recent clinical trials involving drugs acting on the neurotransmitter calcitonin gene-related peptide (CGRP) appear promising. In this article, we review the evidence and critique the new and emerging treatments and give our opinion on how the future in migraine treatment will progress. The invasive surgical treatments of occipital nerve stimulation and deep brain stimulation, used as a last resort, are not discussed in this article.

Pathophysiology of Migraine

The pathophysiology of migraine is not fully understood. In the 1980s, the vascular theory that the migraine aura was due to hypoxemia secondary to vasoconstriction, and that the headache was the result of rebound vasodilatation, gained popularity [4]. However, it became clear that the vascular theory did not explain the headache, and it was shown that reduced blood flow was still present when the headache of migraine with aura had started [5]. The alternative and widely accepted theory suggests that cortical spreading depression (CSD), a wave a neuronal hyperactivity followed by an area of cortical depression, accounts for the aura [6,7] and that the headache depends on activation of the trigeminovascular pain pathway [8,9]. CSD has been studied in animal models leading to an in-depth knowledge of ionic, neurochemical and cellular mechanisms [10]. Induction of spreading depression has been shown to cause vasodilation in meningeal vessels by a reflex dependent of trigeminal and parasympathetic pathways [11]. Several messengers that activate or sensitize pain-signalling pathways have been found in relation to CSD in animal models [10]. A dense network of dural nerve fibres that react with substance P and calcitonin gene-related peptide (CGRP) has been found [12], the role of the latter in the development of new treatments is discussed further in this review. CSD has also been reported to cause changes in brainstem nociceptive neuronal activity even when the trigeminal pathway has been inhibited [13]. In humans, functional imaging has shown changes in cortical function and blood flow and the patterns of spread are suggestive of CSD [10].

Although our understanding of migraine has considerably improved, none of these hypotheses can strictly provide a unifying explanation for this disorder. There is a lack of definitive evidence of CSD in patients with migraines. Unresolved questions surrounding the mechanisms of initiation, continuation, and termination of

migraine as well as how a profound neurophysiological event such as CSD sometimes causes only slight or no neurological symptoms, need to be addressed.

Greater Occipital Nerve Blockade

Peripheral nerve blocks have been practised over the past few years for the management of headache disorders. The greater occipital nerve has sensory fibres originating mainly form the C2 segment of the spinal cord [14]. The effectiveness of GONBs probably arises as a result of its close proximity to the trigeminal afferents [15]. Several techniques to perform occipital nerve blocks exist, and they all appear effective [15]. However, there is a lack of controlled trials to assess its therapeutic benefits in treating migraines; most of them being small and uncontrolled [16,17]. For example, a study of 97 patients with migraine and 87 with post-traumatic headache who had GONB with a combination of lidocaine and methylprednisolone showed a significant improvement in 54% of migraineurs for up to 6 months [17]. Those who display occipital tenderness are more likely to respond [14]. Over the past few years, there has been renewed interest in GNOB. However, despite the fact that it is generally safe, potential side effects such as dizziness, light-headedness and nausea, and rarely cardiac arrhythmias and hypersensitivity reactions, are some limitations to its use [15]. Also, the invasive nature of the procedure makes it less acceptable to patients as a first-line treatment. We nevertheless believe that GNOB is an effective option in a subset of patients with refractive migraine.

OnabotulinumtoxinA

The anti-migraine properties of OnabotulinumtoxinA (Botox®) were incidentally noted in patients who were cosmetically treated for wrinkles, and its efficacy was first shown in an open-label study.[18] Several other trials confirmed these benefits in migraine prophylaxis at the beginning of the 21st century [19,20]. OnabotulinumtoxinA has been around for years and is not a new treatment per se. The phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trial [21] established the role of OnabotulinumtoxinA, as well as its efficacy, in the treatment of chronic migraine (CM) which is defined as a headache on ≥15 days per month for ≥3 months, of which ≥8 days meet the criteria for migraine without aura or responds to migraine-specific treatment [22]. This was the largest clinical program to evaluate the use of OnabotilinumtoxinA in CM. 1384 patients were randomised to either OnabotilinumtoxinA or placebo in the double-blind phase and 1236 patients continued into the open-label phase. Treatment with OnabotulinumtoxinA significantly reduced measures that impact on the patient's ability to function such as headache days, migraine days, headache episodes, and migraine episodes [21]. It eventually gained approval from the Medicine and Healthcare Regulatory Agency (MHRA) in the UK, and the Drugs and Food Administration (FDA) in the USA in 2010. It was recommended for use in the National Health Service (NHS) in the UK by the National Institute of for Health and Care Excellence (NICE) in 2012.

Although critics have commented on a very high placebo response rate in the PREEMPT study and optimal blinding of patients who received OnabotulinumtoxinA and raised eyebrows on the 10% additional improvement over placebo, recently prospective analysis of 254 patients treated with OnabotulinumtoxinA in a real-life setting, demonstrated significantly reduced number of headache and migraine days, and also increased number of headache-free days as well as better quality of life measured through the Headache Impact Test (HIT-6) [23]. Long-term data also suggest that most of those who initially respond will continue to do so for at least two years [24]. There are still some unanswered questions surrounding OnabotulinumtoxinA; for example, whether a subset of patients is more likely to respond than others. Future studies may well address these questions.

Neurostimulation

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) delivers a fluctuating magnetic field from the scalp by which small electrical currents are induced in the brain and this is thought to disrupt CSD [25]. There is robust evidence to suggest that single-pulse TMS (sTMS) is effective as an acute treatment for migraine with aura. In an open label study including 12 patients treated with a portable sTMS resulted in pain freedom in 81% of attacks at 2 hours [26]. In a randomised, sham-controlled involving 42 patients, there was a significantly higher pain relief or pain free rate in the sTMS treated group (69% versus 48%) [27]. These results were confirmed in a larger randomized sham-controlled trial involving 201 patients [28].

If sTMS is effective at treating acute migraine, it can be hypothesized that repetitive TMS (rTMS) may be beneficial in migraine prevention. Indeed, there is promising data to back rTMS as a migraine prophylaxis. The efficacy of high-frequency rTMS was initially demonstrated in a small pilot study where it was compared to sham treatment [29]. Teepker et al. showed a reduction of headache frequency in a study of low-frequency rTMS in 27 patients, but the difference was not significant compared to the sham-treated group [30]. In a randomised, double-blind, palcebo-controlled trial, 50 adult migraineurs having more than 4 attacks in a month were assigned to either high-frequency rTMS or sham treatment [31]. At 1 month, the rTMS-treated group showed a reduction in headache frequency in 78.7% compared to 33.3% in those receiving sham.

Data acquired through years of use of TMS suggest that it is safe. Seizure is rare in patients who use sTMS and is the only adverse event experienced with rTMS to be concerned about, but again the risk is very low [32]. Due to its interaction with some metals, it should be avoided in patients with ferromagnetic implants.

The device works through activation by a SIM card similar to what is used in mobile phones [33]. The consumer pays for the SIM card while the device remains the property of the manufacturer. The treatment is costly and although NICE has recommended the treatment, it is yet to be funded in the public sector in the UK. The main disadvantage of sTMS is the size of the device, although with time this is likely to be reduced as we have seen with mobile technology.

Supraorbital Transcutaneous Stimulator (STS)

Peripheral nerve stimulation involves the exogenous application of electrical current as a method to influencing and abolishing pain signals. It is an accepted treatment for chronic pain. The first case of intractable cluster headache responding to supraorbital nerve stimulation was published in 2007. In combination with occipital nerve stimulation, it was used to treat CM in 14 patients with 71% achieving a 50% or greater decrease in pain severity [34]. The Prevention of Migraine using the STS Cefaly (PREMICE Study) was a randomized, sham-controlled trial assessing the efficacy and safety of

trigeminal neurostimulation with a supraorbital transcutaneous stimulator (STS) [35]. 67 patients were assigned to either verum or sham stimulation with the stimulator applied for 20 minutes daily for 3 months. The primary outcome of 50% responder rate was significantly higher (38.1%) in the verum group than in the sham group (12.1%). In a patients' satisfaction survey involving 2313 participants, the Cefaly® device was found to be safe and was well-tolerated with 53.4% of patients willing to purchase the device [36]. In March 2014, the U.S Food and Drug Administration (FDA) granted approval for the marketing of Cephaly®. The device is small and reasonably priced [37]. This is currently being appraised by NICE although funding through the NHS remains doubtful.

Non-Invasive Vagal Nerve Stimulation

The benefits of vagal nerve stimulation (VNS) in treating migraine attacks were incidentally noted while treating patients with intractable epilepsy [38,39]. However, the invasive nature and potential complications of this procedure has significantly limited its use. Gammacore® is a portable non-invasive VNS (nVNS) that transmits a small electrical signal to the vagus nerve through the skin when held against the neck [40]. In an open-label pilot study including 27 patients using nVNS to treat acute migraine, 21% were pain-free at 2 hours while 42% reported an improvement [41]. Raneiro et al. treated 15 patients (362 attacks) with CM and medication overuse headache (CM/MOH) using nVNS [40]. At two hours, pain freedom was achieved in 121 treated attacks (33.4%). A significant response was observed in 50% of patients. These data are promising, but larger studies are needed before any meaningful conclusions can be drawn.

Calcitonin Gene-related Peptide

CGRP receptor antagonists

Calcitonin gene-related peptide (CGRP) is a multifunctional peptide [42]. The role of CGRP became evident when raised plasma levels were found in the external jugular veins of humans and cats during the activation of the trigeminovascular system [43]. Intravenous administration of CGRP was found to precipitate migraine-like headaches [44]. The mechanisms by which it does so remain uncertain. Subsequently, CGRP receptor antagonists (olcegepant and telcagepant), otherwise known as the 'gepants', were designed for relieving pain during acute migraine and they showed similar efficacy to triptans [45,46]. Olcegepant is only available as an intravenous infusion, therefore restricting its use to inpatient settings. Telcagepant was the first orally available 'gepant' showing consistent efficacy in treating multiple migraine attacks compared to placebo [47,48]. However, daily administration of telcagepant for migraine prevention was associated with hepatotoxicity [49], leading to concerns regarding its safety and eventually to its discontinuation, along with two other drugs of its class (MK-3207 and BI44370A). BMS-927711 has recently been shown to be effective at multiple doses in a Phase 2b trial with a commendable tolerability profile [50] but its long-term safety profile, especially with liver toxicity, is yet to be ascertained. Further plans for BMS-927711 have not been announced but we probably have not heard the last of the 'gepants'.

Antibodies against CGRP and its Receptor

Given its pathophysiological role of CGRP in migraine, disruption of the CGRP pathyway should theoretically be effective in treating the condition. Monoclonal antibodies (mAb) targeting the CGRP pathway represent an attractive prospect for migraine treatment. Biologics have a long half-life, and therefore can be administered infrequently. Furthermore, they can be designed to have precise action and thus minimise side-effects [51].

Four mAbs targeting CGRP have been developed, none of which has completed phase III trial. LY2951742, a humanized mAb aimed at CGRP, has completed phase IIa, double-blind, randomised, placebo-controlled trial in 217 sufferers of episodic migraine [52]. Participants were assigned to either biweekly subcutaneous injections of LY2951742 or placebo, for 3 months. The authors report two serious adverse events in the treatment arm, none of which were attributable to the drug. AMG 334, on the other hand, targets the CGRP receptor and has completed three phase I trials, although the data have not been disclosed, and it is currently undergoing phase II randomized, double-blind, placebo-controlled study in episodic and chronic migraine, with the primary outcome being a change in monthly migraine days from baseline [53]. ALD403, another humanized mAb, is administered intravenously. In a multicentre trial involving 163 episodic migraineurs, ALD403 has been found to reduce migraine days compared to placebo [54]. Full results of the trial are awaited. Finally, LBR-101, a fully humanized mAB, is being tested for both episodic and chronic migraine prevention in two phase IIb trials [55]. Safety profiles, when studied in rats and monkeys, were excellent.

Conclusion

The last few years have witnessed a trend change towards non-pharmacological therapeutic approach for the treatment and prevention of migraine attacks. There has also been more emphasis on prophylactic approaches with OnabotulinumtoxinA, neurostimulation devices and CGRP monoclonal antibodies bieng valuable additions. The main concern lies with the costs of treatment particularly for the funding authorities, although as with many other technologies, cost reduction comes with increased usage, and commissioners will have to acknowledge the changing trend.

Conflict of Interests

Rubesh Gooriah has none to declare.

Fayyaz Ahmed has received honorarium to deliver training workshops for Allergan paid to British Association for the study of headache (BASH) and received honorarium to attend Allergan Advisory Board meetings.

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