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OnabotulinumtoxinA in Migraine and Other Headaches: Review and Update

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Abstract

Purpose of the review The role of onabotulinumtoxinA in headache management was serendipitously found over a decade ago and approved for chronic migraine in 2010 based on pivotal studies. The purpose of this review is to highlight the impact on headache and other health parameters which is critically reviewed, as well as the putative mechanisms of action.
Recent findings OnabotulinumtoxinA is effective in migraine, not only headache frequency and pain intensity but also other health parameters including quality of life. Tolerability is high and benefit/cost analysis is favorable. It should be considered off-label in refractory trigeminal neuralgia and post-herpetic neuralgia but further research in these areas. Ongoing investigation of onabotulinumtoxinA in cluster headache is too preliminary for recommendation of use but promising. Recent and future developments in other headache disorders are discussed.
Summary OnabotulinumtoxinA has been approved for migraine almost a decade ago and been proven beneficial not only on headache parameters but other health outcomes. Its role as adjuvant is being studied and emerging in other headache syndromes.

Introduction

The diagnosis of migraine is based on clinical criteria stipulated in the *International Classification of Headache Disorders and Facial Pain, Third Edition* (Headache Classification Committee of the International Headache Society) [1]. In the classification, migraine is the first primary headache category and chronic migraine is the third subcategory (diagnostic code 1.3). To qualify for the chronic form of migraine, one must have headaches at least 15 days/month and specifically headaches with migraine features more than half of those days (min 8 days/month). A common risk factor for the chronic transformation of migraine is medication overuse.

When a patient uses relief medication frequently (10 or more days per month for opioids, 15 or more days for most other drugs) and the primary headache syndrome (here, migraine) worsens, it is considered that the patient suffers from medication-overuse headache as well. This clinical situation is especially challenging to treat.

The diagnoses of cluster headache and primary and post-herpetic trigeminal neuralgia are likewise diagnosed clinically according to criteria in the aforementioned classification [1]. They are also particularly disabling conditions and treatment options need improvement and innovation.

We hereby reviewed the literature with the aid of PubMed search on the role of onabotulinumtoxinA in headache disorders since its initial development with emphasis on a critical review of the pivotal studies as well as on the novel understanding and approaches in the last 3 years.

Review in migraine

Chronic migraine prophylaxis is classically based, by extension, on studies performed on episodic migraine. Besides onabotulinumtoxinA, only a few prophylactic agents have been submitted to specific studies in populations of pure chronic migraineurs, including topiramate and the newer monoclonal antibodies targeting CGRP (calcitonin-gene-related peptide) or its receptor, namely erenumab, fremanezumab, and galcanezumab [2–6].

OnabotulinumtoxinA has been used in the management of movement disorders and especially cervical dystonia, for decades. Serendipitously, migraine sufferers treated for cervical dystonia with onabotulinumtoxinA reported improvement in their migraine symptoms [7]. Soon, a first randomized, placebo-controlled study of 123 subjects with migraine appeared to show benefit of a small dosage on onabotulinumtoxinA injection in the forehead [8].

OnabotulinumtoxinA has been approved in 2010 for the prophylaxis of chronic migraine, with or without medication-overuse headache, based on two large multi-centric, randomized, pivotal trials called PREEMPT (Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy), with a placebo-controlled 6-month phase followed by an 8-month open-label phase [9••, 10••].

The following summarizes the salient features of PREEMPT studies. Subjects suffering from chronic migraine with an average of 20 days of headache per month were randomly and blindly attributed to either 155–195 U of onabotulinumtoxinA or matching saline. The injection sites and dosages are detailed below. Two treatment rounds were given at 12-week intervals. Efficacy assessments of the blinded phase were made comparing the 28-day baseline observation period prior to the first treatment and the 28-day period last preceding week 24. In the PREEMPT 1 study ($n = 671$), the primary outcome measure, headache episode frequency difference between groups, was not found to be statistically significant (– 5.2 (from 20.0) for the onabotulinumtoxinA group, – 5.3 (from 19.8) for the placebo group). As to the secondary outcome measures, the frequency of headache days and that of migraine days significantly improved on the onabotulinumtoxinA group compared with the placebo group (– 7.8 vs – 6.4, and – 7.6 vs – 6.1, respectively); however, the frequency change in migraine episodes and the change in number of days using relief medication were not statistically significant. Likewise, functional impact measures of HR-QoL (health-related quality of life) by HIT-6 (Headache Impact Test), HIS (Headache Impact Score), and MSQ (Migraine-

Specific Quality of life questionnaire) showed statistically significant benefit. In the PREEMPT 2 study ($n = 705$), the primary outcome was the change in monthly headache days and it was statistically significant: decreased by 9.0 from 19.9 in the verum group and by 6.7 from 19.7 in the placebo group. The secondary measures included the change in migraine days, in headache episodes, and in the frequency of moderate-to-severe headaches; the change in cumulative headache hours; the change in percentage of patients with severe HIT-6; and the improvement in HR-QoL by tools similar to those used in the PREEMPT 1. All these secondary measures were found statistically significant, favoring onabotulinumtoxinA. The additional secondary outcome of change in frequency of use of relief medication was not significant. Tolerability of onabotulinumtoxinA in the PREEMPT trials is high. Treatment-emergent adverse events occurred in 25 and 33% patients (respectively for PREEMPT 1 and PREEMPT 2), and the only ones above 5% were injection site weakness (5.9 and 5.2%) and pain (5.9 and 7.5%). Other than one case of hospitalization for migraine, no serious adverse events linked to treatment were noted.

The relative reduction in headache days by 1.4 and 2.3 when comparing the onabotulinumtoxinA group to the placebo group may seem clinically mild yet keeping in mind the therapeutic challenge of chronic migraine, it does appear meaningful. The functional benefit on the HR-QoL reflects real-world common impression by patients that even if there are still often a large number of headache days, the pain is significantly less impacting and their ability to increase and diversify their activities is perceptible.

In the experience of the authors and accounts of colleagues, the onset of clinical action of onabotulinumtoxinA is between 1 and 2 weeks after injection and the efficacy starts partly fading down after approximately 10 weeks but there is high variability between patients.

The high level of placebo effect is not unexpected, being common in headache conditions and high with procedures overall. The difference in improvement on the verum vs on the placebo seems to continue through the 6 blinded months of PREEMPT studies, but the placebo appears to persist when outcome measures are compared to baseline. Therefore, caution must be exerted when interpreting results. Placebo concept put apart, the number of monthly headache days under treatment is clinically significant, giving an opportunity for increased daily life activities and comfort.

The knowledge of distribution and dosage of injections of onabotulinumtoxinA has benefited from dose-ranging studies as well as various distribution schemes in studies previous to PREEMPT 1 and 2 [11, 12]. In PREEMPT trials, most patients were administered fixed doses in fixed 31-point distribution except in a small proportion of separately analyzed patients. In them, the efficacy and tolerability of added 10–40 U (units) (to a total of max 195 U) were evaluated; additional occipitalis, temporalis, and trapezius injections can be individually clinically justified in unusual circumstances involving significant focalization of pain in those areas [13]. This classically used paradigm of injections based on the PREEMPT studies is described in Table 1.

With more understanding of the mechanism of action especially the importance of neuromodulation, it may seem attractive to target specific nerves rather than muscle areas. Some attempts in that direction have been reported albeit based on questionable premises of efficacy of nerve-

Table 1. Injection protocol according to PREEMPT studies

Injection muscle area	Standard no. of injections	Potential additional follow-the-pain injections
Procerus	1 (midline)	
Corrugator	2	
Frontalis	4	
Temporalis	8	2
Occipitalis	6	2
Semispinalis	4	
Trapezius	6	4
Total	31	
Total no. of U	155	40 (to grand total 195)

Injection distributions: each injection 5 U (units); 30-G needles are recommended; used for no more than 6 injections in order to minimize pain risk from blunted needles. Procerus and corrugator have to be injected very superficially to avoid affecting the lower frontalis which can result in brow ptosis

targeting surgical treatment of migraine [14]. Proper, rigorous studies rooted in migraine pathogenesis are warranted to address this issue.

As stated earlier, chronic migraine is a very challenging condition to manage and long-term improvement a difficult goal to achieve. Commonly, tachyphylaxis sets in. Moreover, compliance with treatment remains low, lowering therapeutic outcomes. Since approval of onabotulinumtoxinA for the prophylaxis of chronic migraine, several trials have established long-term efficacy and low likelihood of tachyphylaxis. Besides significant improvement in headache symptoms, well-being, and functional ability in chronic migraine, it is encouraging to observe no significant tachyphylaxis of onabotulinumtoxinA overall, but rather accrual of efficacy over a number of injections. The aforementioned PREEMPT trials have demonstrated persisting efficacy during the 32-week extension open-label phase. Interestingly, patients who were in the initial double-blind 24 weeks, randomized to placebo, subsequently improved after starting the onabotulinumtoxinA in the open label, with outcome numbers increasingly closer to those patients in the initial onabotulinumtoxinA group. This is further confirmed when data from the PREEMPT 2 studies are pooled [15]. The persisting therapeutic benefit is also clearly shown in a 2-year open-label, prospective, multi-centric study of onabotulinumtoxinA with PREEMT protocol; the remanence of efficacy on headache parameters as well as patients' functional ability is demonstrated [16]. Similar observations are reported in a retrospective study ($n = 47$) which highlights an accrual of benefit at 18 months over that at 12 months [17]. A retrospective uncontrolled study of onabotulinumtoxinA treatment in a cohort of 90 chronic migraineurs with medication-overuse headache shows efficacy as well as consistency thereof, with measures of headache parameters, disability, and additional health measures including assessment of depression [18] (Fig. 1).

Due to the significant cost of onabotulinumtoxinA in migraine care, the issue of cost-effectiveness has been raised. When factoring efficacy on headache-specific outcomes (headache frequency, headache intensity), broader measures of function as well as quality of life such as HIT-6 (Headache Impact Test) and HR-QoL

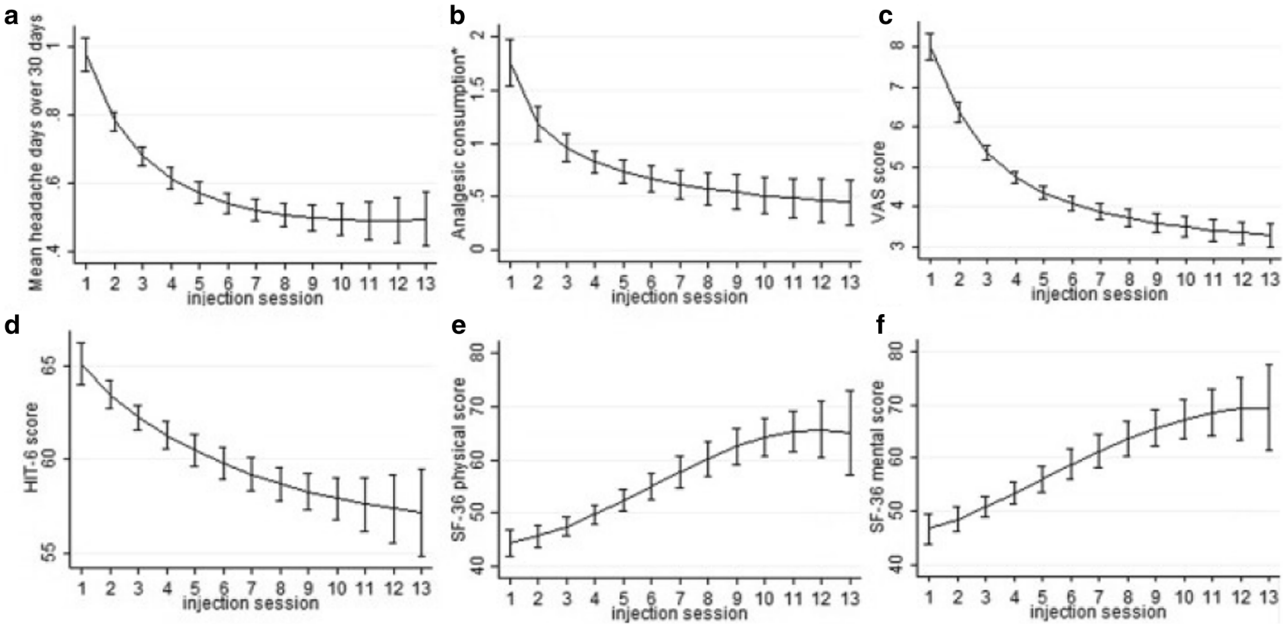

Fig. 1. Benefit of onabotulinumtoxinA in the long term. Outcomes over time across 13 sessions (3 years) of PREEMPT protocol onabotulinumtoxinA injections: **a:** headache frequency; **b:** relief medication usage; **c:** pain visual analog scale; **d:** HIT-6 (headache impact test); **e:** SF-36 (short form 36) physical; and **f:** mental scores. The graphs highlight the accrual of benefit over time, more prolonged initially than at later stages (see text for details) [18].

(migraine-specific health-related quality of life assessment), healthcare resource utilization such as urgent care, and productivity impact such as absenteeism, onabotulinumtoxinA use for migraine appears to remain cost-effective [19, 20].

Medication-overuse headache is often superimposed to chronic migraine and worsens its prognosis and makes its management much more challenging. Fortunately, onabotulinumtoxinA seems to remain efficacious in migraine when medication-overuse headache is present. This is suggested in the PREEMPT studies (although not a predetermined outcome measure) as well as an open-label prospective evaluation of 155 patients over 2 years [21]. A large retrospective survey of patients with moderate-to-severe depression undergoing onabotulinumtoxinA for chronic migraine management ($n = 127$) showed improvement not only of the headache parameters and those of quality of life, but of the depression itself [22]. The study was not set to assess the effect of headache improvement as a potential culprit for the improvement in mood.

The prospect of injection of onabotulinumtoxinA directly onto the sphenopalatine ganglion is an attractive way to approach migraine treatment by its autonomic end. A prospective, open-label, uncontrolled study showed 8 out of 10 patients injected with 25 U in each ganglion had 50 or more % improvement in headache days at 2 months [23]. Randomized, controlled studies are warranted.

Besides FDA-approved indication for overall chronic migraine, determining which patients might be best responders remains a complex issue. Predictors include a less disabling syndrome, milder intensity, and unilateral distribution of headaches, as well as shorter duration of disease, validating an aggressive prophylactic approach [24].

Pathophysiology

The mechanism of action of onabotulinumtoxinA in ha, and in pain in general, remains putative.

Decreased synaptic vesicle release of acetylcholine by blockade of the synaptosomal nerve–associated protein 25 (SNAP-25) may play an essential role in reducing the activity of the trigeminal pathway centripetally.

Peripherally, onabotulinumtoxinA putatively modulates neurogenic inflammation by affecting the release of substance P, Neurokinin A, and even CGRP [25].

Glutamate contributes to peripheral neurogenic inflammation, and its release is apparently reduced by onabotulinumtoxinA including by satellite ganglion cells [26, 27].

OnabotulinumtoxinA diminishes central sensitization by affecting the activity of transient receptor potential cation channels TRPV1, TRPV2, and TRPA1 [28, 29].

Although there is no evidence of central nervous system penetration, onabotulinumtoxinA also affects neuronal trafficking, thereby indirectly modulating CNS activity [30].

Practical considerations in treatment implementation

OnabotulinumtoxinA is manufactured by fermentation of *Clostridium difficile*, precipitation, and filtration of the toxin off the medium, then vacuum-dried processed (Product Information Package Insert, Irvine, Calif, Allergen, Inc., 2002).

Local anesthetic with lidocaine cream can offer some relief from injection site pain but the benefit remains marginal and should not be considered as routine practice [31].

The advent of CGRP-directed monoclonal antibodies in the armamentarium of migraine therapy may change the role of onabotulinumtoxinA in migraine. However, the indications partially differ (the latter is solely indicated for chronic migraine, whereas the formers are for episodic as well as chronic migraine); the duration of experience is vastly different; the difference in known or suspected mechanisms of action make the comparison limited. They should be viewed as independently beneficial.

The method of injection of onabotulinumtoxinA in chronic migraine prophylaxis is explained in the PREEMPT trials. Further discussion is detailed by Blumenfeld [13]. The table elaborates on the injection scheme outline.

Injections are performed on average every 3 months yet some patients may benefit from onabotulinumtoxinA for a longer period; thus, the frequency can be accordingly somewhat adjusted; shorter duration of action could also lead to higher frequency of injection but insurance coverage is typically not supportive.

Therapeutic benefit may not be readily apparent for the first few weeks; hence, two sets of injections and observation at 6 months are recommended before considering discontinuation due to inefficacy.

Side effects can include local effects: injection site weakness manifested as decreased facial expression, eyebrow and eyelid ptosis, dysphagia, xerostomia, injection site reaction (pain, infection, weakness) as well as, especially in

emaciated patients, pneumothorax (trapezius sites); distant: systemic spread of the toxin with fatigue, generalized weakness, and hypersensitivity. The side effects seem to be transient (up to about 4 months, matching biological activity) and most require reassurance or local measures, by contrast to pneumothorax and hypersensitivity which are serious.

Formal contraindication is known as hypersensitivity to onabotulinumtoxinA. No absolute contraindication but caution should be exerted in the case of neuromuscular junction defect (myasthenia gravis, aminoglycosides, etc.), possible local infection, devices such as shunts, and anticoagulation therapy.

In the USA, the reimbursement of onabotulinumtoxinA injections for chronic migraine by private health insurance companies, and government coverage agencies alike, typically requires prior failure of 2–3 other prophylactic agents.

Review in other headaches and cranial neuralgias

Per several randomized, controlled trials, tension-type headache does not benefit from onabotulinumtoxinA [32, 33].

Investigations of onabotulinumtoxinA in cluster headache have been recently initiated. An open-label trial of 17 patients with refractory chronic cluster headache used the PREEMPT protocol of onabotulinumtoxinA treatment. After 24 weeks, 59% patients had at least 50% reduction in attack frequency; the average monthly attack frequency decreased from 28 to 12; no serious adverse event was reported [34]. In a prospective uncontrolled trial on 7 patients with refractory chronic cluster headache, 25 or 50 U of onabotulinumtoxinA were serially injected, every 3 months for 18 months, directly onto the ipsilateral sphenopalatine ganglion with a novel, infra-zygomatic, transcutaneous device using surgical navigation. Average monthly attack frequency decreased from 57 to 12 at 12 months and 25 at 18 months; 5 of the 7 patients reported at least 50% improvement in a weekly attack frequency at 12 months and 4 patients did at 18 months; no serious adverse event was reported [35•].

Comparing younger and older patients, similar efficacy was found in 43 trigeminal neuralgia sufferers; using onabotulinumtoxinA in the range of 70–95 U distributed among the branches of the trigeminal nerve areas ipsilateral to the pain, the visual analog scale was reduced by approximately 40% at 1 month [36].

Evidence of efficacy of onabotulinumtoxinA in the treatment of trigeminal neuralgia is considered class I [37].

A randomized, placebo-controlled trial of 30 patients with post-herpetic neuralgia showed significant evidence of efficacy of one-time 100 units of onabotulinumtoxinA injected in the symptomatic area on visual analog scale as well as an improvement in sleep quality [38].

OnabotulinumtoxinA is emerging as a significant player in the armamentarium of pain management, especially modulation of sensitization and neurogenic inflammation [39].

Conclusion

In conclusion, chronic migraine, cluster headache, and trigeminal neuralgias are undeniably very disabling conditions and their management, although vastly

improved to this day, remains extremely challenging and continues to justify developing better options. The role of onabotulinumtoxinA in the management of migraine has been serendipitously discovered and its indications refined. The classic PREEMPT-based protocol is recommended and allows some flexibility. However, it is conceivable that, with further understanding of the mechanism of action, a modification of protocol targeting nerve structures rather than muscle groups may emerge but would require undertaking in-depth large studies for validation. Safety and tolerability of this treatment is consistently high. The benefit not only on headache parameters but also on other related health parameters and quality of life has been highlighted. Novel methods of administration are being studied. Additional benefit is being investigated with some emerging evidence, in other headache disorders that include cluster headache, trigeminal, and post-herpetic neuralgias. Taken altogether, this might open a new chapter in the story of onabotulinumtoxinA in headache disorders.

Compliance with Ethical Standards

Conflict of Interest
Marc Lenaerts is a member of Speakers Bureaus of Amgen, Allergan, and Teva Pharmaceuticals. Tiffany Green declares no potential conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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