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Review Article

OnabotulinumtoxinA (Botox) in Chronic Migraine: A Review

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Abstract

Migraine is a chronic disabling neurological disease that can evolve from episodic migraine to chronic migraine (CM). Chronic migraine is seen in about 2% of the patients' worldwide. CM is one of the most disabling forms of migraine, affecting the quality of life of the patients' and it places excessive financial burden on the health industry as well as the society. There are reports that despite the available evidence only one third of patients with CM receive appropriate treatment. OnabotulinumtoxinA injections given every 12 weeks at fixed dose and fixed sites have been proven to be safe and efficacious in the prophylactic management of CM. OnabotulinumtoxinA has been shown to be superior to placebo in the randomized control trials in improving the quality of life in patients with CM. There is also data to show meaningful proportion of patients who do not respond to the first time treatment with onabotulinumtoxinA injections do respond to the subsequent treatment schedules. The purpose of this review is to represent an overview of the current literature and evidence available in the management of debilitating CM based on the literature search through PubMed, MEDLINE, EMBASE and the Cochrane databases published in English language between 1995 to 2017.

Keywords: *Migraine; OnabotulinumtoxinA; Chronic Migraine; Headache*

Abbreviations

CM: Chronic Migraine; PREEMPT: The Phase III REsearch Evaluating Migraine Prophylaxis Therapy; (HRQoL): Health-Related Quality of Life; HIT-6: Headache Impact Test; (MSQ): Migraine Specific Quality of Life Questionnaire

Introduction

Migraine is one of the commonest primary headache encountered in the clinical practice along with chronic daily headache and tension headache. It is amongst the top 10 disabling neurological disorder worldwide [1,2].

Migraine headache is clinically characterized by unilateral, throbbing pain, associated with nausea and/or vomiting, and photo- and phonophobia [3]. It is classified by the international headache classification into multiple subtypes and categories, but of all those sub classifications, the clinicians in their practice are likely to deal commonly with migraine with aura which is associated with transient focal neurological symptoms that usually precede or accompany the headache; migraine without aura which is characterized by specific features and associated symptoms as noted above; episodic migraine that is characterized by headache lasting 4 - 72 hours on < 15 days a month associated with lateralized pulsating pain, which worsens by routine physical activity, nausea, photophobia, and/or phonophobia as well as chronic migraine (CM) which is defined as headache occurring on ≥ 15 days per month for more than 3 months, along with associated features of migraine headache on 8 days. Chronic daily headache encompasses chronic migraine, hemicrania continua, new daily persistent headache, chronic tension-type headache and medication overuse headache.

CM affects about 2 percent of the world population [4]. Approximately 3% of episodic migraine evolve into chronic migraine [3]. CM affects the quality of life significantly, with reduced health-related quality of life (HRQoL) and is more disabling than episodic migraine [5-

8,9]. In addition to quality of life, CM increases the financial burden on society as well as the patients. It has been reported that migraine in the United States costs about 20 billion dollars annually of which a significant proportion is attributable to CM [10].

Pathophysiology of Chronic Migraine

Pathophysiology of CM includes alterations in periaqueductal gray matter iron homeostasis, with possibly progressive increased activity in pons and other areas in interictal period as well as excessive baseline cortical hyperexcitability and more substantial alteration in brain processing of cutaneous pain, but while compared to CM in episodic migraine there is only some baseline cortical hyperexcitability. Also in episodic migraine triptans and topiramate are usually effective while with CM triptans are frequently ineffective while topiramate may be effective but onabotulinumtoxinA is proven efficacious and tolerable [11-16].

As noted above about 3% patients with episodic migraine gets transformed to CM. Higher risk of such transformation is seen with nonmodifiable risk factors like female sex, lower socioeconomic status, unmarried population while the modifiable risk factors associated with such transformation are acute headache medication use, caffeine intake, obesity, other pain syndromes, previous head or neck injury, snoring, and stressful life events [17]. It has also been reported that headache frequency is also an important risk factor for progression as it has been determined that individuals with ≥ 4 headache days per month have increased risk of transformation from episodic to CM [18,19].

PREEMPT 1

The Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) was a randomized control study to evaluate the safety and efficacy of OnabotulinumtoxinA in the prophylactic management of CM. It consisted of 2 phase 3 trials PREEMPT 1 and PREEMPT 2.

In PREEMPT 1 OnabotulinumtoxinA was compared to placebo and it had a 24 week double blinded placebo controlled phase followed by a 32 week open label phase. Patients were randomized 1:1 to receive OnabotulinumtoxinA injections every 12 weeks or placebo treatment. The primary endpoint was mean change from baseline in headache episode frequency at week 24. The secondary endpoint was mean baseline decrease in frequency of headache days, migraine days, migraine episodes and acute pain medication intake. PREEMPT 1 was conducted from January 2006 to July 2008 and enrolled 679 patients who were randomized to OnabotulinumtoxinA (n = 341) or placebo (n = 338). There was no observed difference between the groups in mean change from baseline in frequency of headache episodes at 24 weeks for primary end point. But the post hoc analysis of headache episode frequency favored OnabotulinumtoxinA over placebo at 4, 8, 20 and 24 weeks. Secondary efficacy endpoints showed a statistically significant decrease in the frequency of headache days and migraine days. The study did observe improvements in frequencies of migraine episodes and acute pain medication intake though it was not statistically significant. It was also observed in this study that OnabotulinumtoxinA significantly decreased the disability and improved the functioning when compared to placebo [20]. The authors concluded that OnabotulinumtoxinA may be effective in treating refractory analgesic overuse headache as well as was superior to placebo as it decreased the baseline headache days, migraine days as well as reduced disability in patients with CM.

PREEMPT 2

In PREEMPT 2, the second of the pair of studies, OnabotulinumtoxinA was compared to placebo and it also had a similar 24 week double blinded placebo controlled phase followed by a 32 week open label phase. Patients were randomized 1:1 to receive OnabotulinumtoxinA injections every 12 weeks or placebo treatment. The primary endpoint was mean change in headache days from baseline to weeks 21 - 24 after treatment. The secondary endpoint was mean baseline decrease in frequency of migraine days, frequency of moderate/severe headache days, acute pain medication intake and disability assessment. PREMPT 2 was conducted between February 2006 to July 2007 and enrolled 705 patients who were randomized to OnabotulinumtoxinA (n = 347) or placebo (n = 358). OnabotulinumtoxinA was superior to placebo and there was statistically significant decrease in frequency of headache days from week 4 through 24 week for primary end point. Secondary efficacy endpoints showed a statistically significant decrease in the frequency of migraine days, frequency of moderate/severe headache days, cumulative total headache hours on headache days, and headache impact test scores from baseline.

The study did observe improvements in frequencies of acute pain medication intake though it was not statistically significant. It was also observed in this study that OnabotulinumtoxinA significantly decreased the disability and improved the functioning when compared to placebo [21]. The authors concluded that OnabotulinumtoxinA was superior to placebo in the prophylactic management of CM.

In both the PREEMPT 1 and 2 studies more adverse events were noted in the OnabotulinumtoxinA group as compared to placebo but most adverse events were mild to moderate in severity and resolved without any sequelae. There were no deaths reported in the OnabotulinumtoxinA group. The commonest adverse events noted during the study were neck pain and muscle weakness which were reported to occur in more than 5% patients. But authors reported that discontinuation of OnabotulinumtoxinA due to adverse events was very low in the study and concluded that 2 cycles of treatment with 155 - 195 units of OnabotulinumtoxinA was safe and well tolerated.

Botox as treatment for Chronic Migraine.

One of the recent theories proposed in the pathophysiology of migraine is cortical spreading depression (CSD) which is a slow depolarization of the neuroglial elements along with the depression of electroencephalographic activity [22]. Recent studies have suggested that in migraine calcitonin gene-related peptide (CGRP) plays an important role in the peripheral and central sensitization in the trigeminal vascular system including the trigeminal ganglion [23-26]. CGRP is found mainly in the dorsal root ganglia as well as in the trigeminal ganglia [27-29]. CGRP release may be inhibited by onabotulinumtoxinA and this in turn may exert analgesic effect seen in CM [30]. The mechanism of action of onabotulinumtoxinA in CM includes the inhibition of calcitonin gene-related peptide and substance P release in the trigeminovascular system [31,32]. At the neuromuscular junction when there is calcium influx it will lead to exocytosis of vesicles containing acetylcholine. OnabotulinumtoxinA acts on the neuromuscular junction and cleaves the soluble N-ethylmaleimide-sensitive factor (NSF)-attachment protein receptor complex (SNARE)-like synaptosomal-associated protein of 25 kDa (SNAP-25) [33,34]. This in turn will prevent the exocytosis of the vesicles into the synaptic cleft. With many sympathetic C fibers acetylcholine is co-localized with CGRP. This action of OnabotulinumtoxinA results in the inhibition of the release of CGRP, substance P and glutamate [34].

OnabotulinumtoxinA was initially reported to help headache in those patients who received it for cosmetic treatment of facial wrinkles [32,35]. Following which different trials reported its efficacy in treatment of chronic daily headache, tension-type headache, episodic migraine as well as CM [35]. As discussed above PREEMPT-1 and PREEMPT-2 studies demonstrated that treatment with OnabotulinumtoxinA was superior to placebo in reducing headache frequency as well as was safe and well tolerated as a prophylactic management of CM [35-38]. Based on the PREMPT I and II results, in October 2010, the United States Food and Drug administration approved onabotulinumtoxinA (155 - 195 U) intramuscular injection for preventive treatment for CM [39].

For CM management onabotulinumtoxinA is administered at fixed sites at fixed dose intramuscular injections with a 30 gauge 0.5 inch needle at an angle of 45 degrees to the muscle plane and it is scheduled to be repeated every 12 weeks [31,37]. It is injected at 31 injection sites across the head and neck regions [40,41]. The recommended fixed-sites and fixed-doses (totally 155 - 195 units (U)/cycle) are: corrugator muscle: 5 U (each side), procerus muscle: 5 U (one side), frontal muscle: 10 U (each side), temporalis muscle: 20 U (each side), occipitalis muscle: 15 U (each side), cervical paraspinal muscle: 10 U (each side), trapezius muscle: 15 U (each side) [31]. U is an estimated dose that is lethal to 50% of mice when the toxin is injected intraperitoneally [33]. OnabotulinumtoxinA is thought to affect the branches of trigeminal nerve, occipital nerves as well as sensor rami of the C3 - C5 cervical spinal segments [31].

As discussed above CM poses a huge financial burden on the patient and the society but Rothrock., *et al*. reported that onabotulinumtoxinA treatment in CM reduced the emergency department as well as urgent care visits and hospitalization for migraine in the initial 6 months after starting the treatment and thereby offsetting the enormous financial burden of CM [42]. OnabotulinumtoxinA also improves the quality of life. Lipton., *et al*. reported that OnabotulinumtoxinA improves the quality of life over the entire year of treatments as suggested by persistent benefits on HRQoL that throughout the year of treatment, improvement in headache impact test (HIT-6) demonstrated in the treatment group over 48 weeks while for migraine specific quality of life questionnaire (MSQ) the benefit persisted over 56 weeks in the treatment group as compared to placebo [43].

Conclusion

OnabotulinumtoxinA treatment should be offered to patient population with CM who have failed medical therapy with antiepileptics, antidepressants and beta blockers, given the robust data for safety and efficacy of onabotulinumtoxinA in prophylactic management of CM and also since data suggests that onabotulinumtoxinA improves quality of life and decreases the financial burden in patients with CM.

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