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Botulinum Toxin Type A for Chronic Migraine

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Abstract Chronic migraine (CM) is the leading cause of chronic daily headache, a common and debilitating headache syndrome. The management of CM patients is challenging, with only limited benefit from available oral preventive medications. Botulinum neurotoxin (BoNT) has been used extensively to treat disorders associated with increased muscle tone. More recent scientific data support an analgesic effect of the toxin. The pharmacokinetic and pharmacodynamic profiles of BoNT make it an appealing candidate for migraine prevention. Results from older clinical trials on the efficacy of the toxin in CM were inconclusive. However, recent trials using more stringent inclusion criteria have shown positive results, supporting the use of the toxin in some patients with this disorder. This review summarizes the scientific data on the analgesic properties of BoNT, as well as the clinical data on the efficacy of the toxin in treating CM.

Keywords Botulinum toxin · Chronic migraine

Introduction

Chronic migraine (CM) is a severe headache syndrome that typically evolves from episodic migraine, and currently is regarded as a complication of this disease [1]. CM is the leading cause of chronic daily headache (CDH), defined as a headache that occurs 15 or more days per month for longer than 3 months, and lasts more than 4 h per day [2]. CDH is a common disorder, with an estimated prevalence of approximately 4% of the adult population worldwide [3]. CDH sufferers comprise the majority of patients seen at specialized headache clinics in the United States [3]. These patients often are significantly disabled and commonly suffer from both medical and psychiatric comorbidities. Overuse of pain medications is a common, albeit not invariable, occurrence in these patients, adding to the complexity of their management.

During the past decade, considerable progress has been made in our understanding of the mechanisms of CDH, particularly the transformation from an episodic pattern of migraine to CDH [4]. The management of CDH patients, however, remains challenging. Several oral preventive medications have been shown to be effective in decreasing headache frequency in CM [5]. However, the clinical improvement in many patients is only moderate. Furthermore, the daily use of headache-preventive medications may be associated with serious adverse effects, such as weight gain, sedation, cognitive impairment, and adverse metabolic effects, resulting in limited compliance in a significant proportion of patients.

Botulinum neurotoxin (BoNT) is a potent toxin produced by the anaerobic bacterium *Clostridium botulinum* [6]. The toxin belongs to the clostridial neurotoxin family, along with tetanus neurotoxin, and exists as seven antigenically distinct serotypes (A–G) [7]. BoNT type A (BoNT-A) is by far the most widely used serotype in clinical practice. BoNT-A affects the nervous system through a multistage process that results in the blocking of neurotransmitter release. The toxin binds to the target nerve terminal and subsequently is internalized. BoNT-A then acts as a zinc-dependent endopeptidase to cleave one or more proteins essential to neurotransmitter release. The muscle relaxation effect of BoNT-A results from its ability

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to block acetylcholine release at the neuromuscular junction. BoNT-A has been used extensively for the past few decades to treat various disorders associated with increased muscle tone, such as cervical dystonia and spasticity. The toxin subsequently has been used effectively in treating some disorders associated with autonomic dysfunction (eg, hyperhidrosis). Support for an analgesic effect of BoNT-A, independent of its muscle relaxation effect, came from clinical observations that some patients with dystonia obtained pain relief before experiencing improvement in muscle tone [8]. BoNT-A also was found to alleviate migraine headache in some patients who were given the toxin to treat facial wrinkles [9]. These observations led to intense efforts to evaluate the analgesic properties of BoNT-A and to assess their clinical applicability.

The pharmacologic profile of BoNT-A makes it an appealing candidate for migraine prevention. Its long duration of action (3 months on average) makes it particularly attractive for patients who are not compliant with, or cannot tolerate, the daily use of oral preventive medications. In addition, the toxin has a favorable adverse effect profile, with little or no effect on weight, alertness, or cognition.

This article summarizes and evaluates the current scientific data on the analgesic properties of BoNT-A and the clinical data on its efficacy in treating CM.

Evidence for an Analgesic Effect of BoNT-A

The analgesic effect of BoNT has been increasingly recognized over the past decade [10]. The toxin can inhibit the presynaptic release of several pain neurotransmitters and has been found to block the release of substance P from rat dorsal root ganglia neurons in vitro [11]. It also has been shown to inhibit the release of glutamate and neuropeptides from synaptosomes [12]. More recently, BoNT-A was shown to suppress the secretion of calcitonin gene-related peptide, a neuropeptide involved in migraine pathophysiology, from rat trigeminal ganglia neurons [13]. Data from in vivo studies further support an analgesic effect of BoNT-A. The toxin was shown to inhibit the delayed nociceptive response of rats, as assessed by reduced pain behavior, after formalin injection [14]. This effect was accompanied by a reduction in formalin-evoked glutamate release from primary afferent nerve terminals. Of note, the analgesic effect of the toxin in that study was achieved at doses that did not cause muscle weakness. In another animal model, it was shown that injecting BoNT into the forehead of rodents prevents sensitization of wide dynamic range neurons in the trigeminal nucleus caudalis induced by applying an inflammatory soup on the dura [15]. BoNT-A also may affect the nervous system through central mechanisms. A recent animal study demonstrated a retrograde axonal transport of catalytically active BoNT-A by central neurons and transfer of the toxin to afferent synapses [16••]. In addition, BoNT-A may affect central nervous system function indirectly, through its modulatory effect on afferent input. It has been shown in animal models that BoNT-A can reduce muscle spindle afferent discharge and cause atrophy of both intrafusal and extrafusal muscle fibers [17, 18].

Data from two recent clinical studies support an analgesic effect of BoNT-A in patients with neuropathic pain [19•, 20•]. In a placebo-controlled study, the effect of intradermal injection of BoNT-A was examined in 29 patients with chronic neuropathic pain and allodynia [19•]. BoNT-A treatment, at a dose of 20 U to 190 U, was associated with an analgesic effect lasting from week 2 to week 14 after injection. BoNT-A also decreased mechanical and thermal allodynia. In the other placebo-controlled study, the effect of BoNT-A on pain was examined in 18 patients with diabetic neuropathy [20•]. BoNT-A was injected intradermally at a dose of 50 U to each foot, and the treatment resulted in a significantly greater decrease of pain, as rated using a visual analogue scale, compared with placebo. The analgesic effect of BoNT-A lasted for the entire follow-up period of 12 weeks. The results of these small studies need to be confirmed in larger clinical trials.

BoNT-A in the Treatment of CM: Data from Clinical Studies

The effect of BoNT-A in patients with CDH was evaluated in several well-designed studies [21–27] (Table 1). Three studies evaluated only patients with CM [25–27]; the other studies included subjects with CDH of various causes, with CM patients comprising a subset of the study sample.

In a randomized, placebo-controlled study, Mathew et al. [21] evaluated the effect of BoNT-A on 355 patients with CDH, most of whom had CM. The authors used the "follow-the-pain" injection approach (ie, they tailored the injection sites and BoNT-A doses for the individual patient according to the location and severity of head pain). Patients were injected three times at 3-month intervals. Although the primary efficacy end point (change from baseline in the number of headache-free days) was not met, BoNT-A treatment was associated with a significant decrease in headache frequency compared with placebo at the 6-month time point (−7.1 vs −3.7 headache days/month with BoNT-A and placebo, respectively). Fifty-four percent of BoNT-A–treated patients reported at least a 50% decrease from baseline in migraine headache frequency, compared with 38% of placebo-treated patients. In addition, BoNT-A

Table 1 Studies of botulinum toxin type A for treating chronic daily headache

Study	Study design	Diagnosis (patients, *n*)	Patients with medication overuse	Injection paradigm	BoNT-A dose, *U*	Results
Mathew et al. [21]	Prospective double-blind randomized placebo-controlled	CDH (355) (Most patients had CM.)	Included	Follow the pain	105–260	Primary end point (change in number of headache-free days) was not met. BoNT-A significantly decreased headache frequency compared with placebo (−7.1 vs −3.7 headache days/month).
Dodick et al. [22]	Prospective double-blind randomized placebo-controlled (A subgroup analysis of the above study for patients who were not on other preventive drugs.	CDH (228)	Included	Follow the pain	105–260	BoNT-A was superior to placebo in reducing the mean frequency and severity of headaches, and in increasing the number of headache-free days/month.
Ondo et al. [23]	Prospective double-blind randomized placebo-controlled	CM (14) CTTH (46)	Included	Follow the pain	200	Primary end point (change in number of headache-free days) was not met. Patients' "global impression" improved with BoNT-A.
Silberstein et al. [24]	Prospective double-blind randomized placebo-controlled	CDH (702) (Most patients had CM.)	Included	Fixed site	75, 150, or 225	Primary end point (change in number of headache-free days) was not met. BoNT-A was superior to placebo in decreasing total headache frequency and migraine headache frequency.
Freitag et al. [25]	Prospective double-blind randomized placebo-controlled	CM (41)	Excluded	Fixed site	100	Primary end point was met: BoNT-A decreased headache frequency significantly more than placebo (−31% vs −9% migraine episodes/ month).
Aurora et al. [26]	Prospective double-blind randomized placebo-controlled	CM (679)	Included	Combination of the 2 paradigms	155–195	No significant benefit of BoNT-A regarding primary efficacy end point (mean change from baseline in number of headache episodes). BoNT-A was significantly superior to placebo in several secondary outcome measures.
Dodick et al. [27]	Prospective double-blind randomized placebo-controlled	CM (705)	Included	Combination of the 2 paradigms	155–195	Primary end point was met: change from baseline in headache days, −9.0 vs −6.7 in BoNT-A and placebo groups, respectively. BoNT-A also was superior to placebo regarding all secondary end points.

(*Adapted from* Ashkenazi et al. [6])

BoNT-A botulinum neurotoxin type A, *CDH* chronic daily headache, *CM* chronic migraine, *CTTH* chronic tension-type headache

decreased the use of acute pain medications, although not significantly more so than placebo. A subgroup analysis of this study's results for the 228 patients who were not taking other migraine-preventive drugs showed a significantly greater decrease in headache frequency (−7.8 vs −4.5 headache days/month, at 6 months) and in mean headache severity in the BoNT-A group compared with the placebo group [22]. The number of headache-free days per month

increased significantly more in the BoNT-A group compared with the placebo arm (+10.0 vs +6.7 days, respectively).

Ondo et al. [23] studied the effect of BoNT-A on 60 patients with CDH, 14 of whom had CM and 46 of whom had chronic tension-type headache. The authors used the follow-the-pain approach to inject 200 U of BoNT-A or placebo at different sites. BoNT-A did not significantly differ from placebo with regard to the primary efficacy end point (the change from baseline in the number of headache-free days over the 12-week study period). However, between weeks 8 and 12, the BoNT-A group had a significantly higher increase in headache-free days compared with those receiving placebo, and there was a tendency for this effect to continue over the entire study period. The global impressions of both the subjects and the investigators were significantly better for the BoNT-A group compared with the placebo group. Women tended to respond better than men to BoNT-A. An open-label extension of the study showed a possible cumulative beneficial effect of BoNT-A on headache. In a randomized placebo-controlled study of 702 patients, Silberstein et al. [24] studied the efficacy and tolerability of BoNT-A for CDH prevention. Most patients for whom a specific headache diagnosis was available had transformed migraine. The authors used a "fixed-site" injection protocol at a total BoNT-A dose of 75 U, 150 U, or 225 U. Patients were given three BoNT-A treatments over a 9-month period. Forty-two percent of the patients were overusing pain medications at the time of the study. The primary efficacy end point (mean change from baseline in the frequency of headache-free days in the BoNT-A vs placebo group) was not met. However, at day 240, patients who received BoNT-A, 225 U, and those who received BoNT-A, 150 U, had significantly fewer headaches compared with patients in the placebo group.

Freitag et al. [25] recently examined the efficacy of BoNT-A in treating CM in a controlled study of 41 patients who did not overuse pain medications. BoNT-A was injected into cranial muscles using a fixed-dose paradigm, at a total dose of 100 U. The treatment resulted in a significantly greater decrease in headache frequency (the primary efficacy end point) compared with placebo (−31% vs −9% migraine episodes per month). BoNT-A was nonsignificantly superior to placebo with regard to the change in quality-of-life measures and Migraine Disability Assessment (MIDAS) scores; in addition, it was well tolerated.

Two recently completed large multicenter, controlled studies—PREEMPT (Phase III Research Evaluating Migraine Prophylaxis Therapy) 1 and 2—evaluated the efficacy and safety of BoNT-A in treating adults with CM. PREEMPT 1, conducted in 56 North American centers, randomly assigned 679 subjects to receive BoNT-A or placebo injections every 12 weeks [26]. Patients who were overusing acute pain medications were allowed to participate, and no patients were using concurrent headache-preventive medications at the time of the study. BoNT-A was injected using a combination of the fixed-site and follow-the-pain approaches, at a total dose range of 155 U to 195 U. The double-blind phase of the study lasted 24 weeks. Despite a large within-group decrease in headache episodes, there was no significant between-group difference with regard to the primary efficacy end point (the mean change from baseline in the number of headache episodes at week 24). However, BoNT-A was significantly superior to placebo with regard to several secondary outcome measures, including the mean change from baseline in the number of headache days and in the number of migraine/probable migraine days, although absolute differences were rather small (−7.8 vs −6.4 and −7.6 vs −6.1, respectively). Patients in the BoNT-A group had significantly less disability, as measured by the Headache Impact Test (HIT-6), and a significantly better quality of life, as measured by the Migraine-Specific Quality of Life Questionnaire. BoNT-A was well tolerated. However, the study was limited by a baseline imbalance in the frequency of headache episodes between the two groups. The similarly designed PREEMPT 2 study was conducted in 66 centers in North America and Europe and included 705 patients [27]. The criteria for patient selection, BoNT-A injection paradigm, and duration of the double-blind phase were similar to those of the PREEMPT 1 study. The primary efficacy end point was the mean change from baseline in the number of headache days (rather than headache episodes) at week 24. BoNT-A was significantly superior to placebo with regard to the primary end point (change from baseline in headache days: −9.0 vs −6.7 in the BoNT-A and placebo groups, respectively). BoNT-A also was superior to placebo with regard to the secondary end points: decrease in headache episodes, number of migraine/probable migraine days, cumulative number of hours with headache during headache days, and number of days with moderate or severe headache. BoNT-A significantly reduced disability and improved quality of life, and was well tolerated.

Critical Assessment of the Data

Basic science data strongly support an analgesic effect of BoNT-A. In accordance with this evidence, many headache clinicians, including the author, have seen patients with CM who have responded dramatically to BoNT-A treatment. However, other patients with CM respond only moderately to treatment, or do not respond to the drug at all. Therefore, patient selection appears to be a key to the successful use of the toxin in headache management. Data from older studies performed during

the past decade were inconclusive. Some of these studies, however, reveal clues as to which subgroups of patients are more likely to respond to treatment with BoNT-A. Indeed, results of the most recent clinical trials, which used more selective inclusion criteria based on data from prior studies, have been more positive. Most notably, the PREEMPT 2 trial showed a positive effect of BoNT-A on headache in patients with CM.

When considering the use of BoNT-A for headache, several factors need to be considered, as described in the following subsections.

Headache Characteristics

In a study of 63 migraineurs, Jakubowski et al. [28] found that patients who described their head pain as pressure from outside ("imploding" headache) or as a feeling of eye popping responded better to BoNT-A than those who described their pain as pressure from inside ("exploding" headache). Mathew et al. [29] looked at predictors of response to BoNT-A in a sample of 82 patients with CDH, most of whom had CM. Predictors of response to BoNT-A in CM patients were unilateral headache, scalp allodynia, and pericranial muscle tenderness.

Disease Duration

It has been shown that CDH patients with disease duration greater than 30 years may be less likely to respond to BoNT-A than those with a shorter disease duration [30]. Selecting patients with shorter disease duration may result in a more robust positive effect of BoNT-A on headache.

Medication Overuse

Patients with CDH who are overusing pain medications often need to be detoxified as part of successful headache treatment [31]. A recent retrospective study showed that patients with CDH who did not overuse pain medications responded more favorably to BoNT-A treatment than those who did [32]. Some studies on the efficacy of BoNT-A for headache included patients who overused pain medications, which may have had a negative effect on the results.

The Use of Concurrent Preventive Medications

Clinical data suggest that patients who do not use concurrent headache-preventive drugs may do better after BoNT-A treatment compared with those who do use these medications [22]. In accordance with these data, the PREEMPT studies, which excluded patients who were using concurrent headache-preventive drugs, showed some of the most positive results with regard to BoNT-A efficacy in CM.

Placebo Response

Analyses of studies on the efficacy of acute oral treatment for migraine revealed an average placebo response rate of 28% to 30% [33, 34]. The placebo response rate in the BoNT-A studies was higher, reaching 50% or more in some studies. As a result, the therapeutic gain of BoNT-A over placebo was modest, although its absolute effect on pain and associated symptoms was substantial. Schwedt et al. [35] looked at predictors of placebo response in patients who participated in a controlled study of BoNT-A for episodic migraine. Male gender, history of opioid use, and injections in the neck/shoulders were associated with placebo response. These findings may help in the design of future studies.

Determining Outcome Measures of Studies

Most experts believe that reductions in headache duration and severity are as important as the mere presence of headache. In many of the older studies, the primary outcome measure was the decrease from baseline in headache frequency, regardless of severity, which may have masked a potential positive effect of the drug on the overall impact of headache in the study populations. The newer PREEMPT studies addressed this issue, looking not only at headache frequency, but also at the frequency of moderate/severe headaches and at disability and quality-of-life measures before and after treatment, as outcome measures.

Treatment-Related Factors

The optimal way to administer BoNT-A for headache prevention has not been determined. Importantly, a dose–response relationship has not been established in this context. In addition, there is no consensus as to the number and location of injection sites, the total dose, and the dose per site. It is not known which of the two commonly used approaches—fixed site or follow the pain—is superior. Recent studies using a combination of these two approaches have shown more positive results, suggesting that this injection paradigm may be preferable.

Conclusions

Scientific data support an analgesic effect of BoNT-A. Clinical experience has shown positive results with the

toxin for some patients with CM. Although data from older studies were inconclusive, results of the most recent studies on the efficacy of BoNT-A for CM have been more encouraging. BoNT-A appears to be effective for some patients with CM. Patients who do not use concurrent preventive medications, and those who have had a relatively short disease duration, may benefit the most from the drug. BoNT-A's long duration of action and favorable adverse effect profile make it particularly suitable for patients who are not compliant with the daily intake of oral headache-preventive drugs. Using BoNT-A for suitable headache patients earlier in the course of their disease, rather than as a last resort, may result in better treatment outcomes. The challenge for future studies is to gain better understanding of the mechanisms of action of BoNT-A in migraine, and to further identify predictors of response to this drug.

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