Botulinum Toxin Type A (BOTOX) for Treatment of Migraine

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An open-label study and 2 double-blind, placebo-controlled studies have provided supporting evidence of botulinum toxin type A (BTX-A) as an effective, well-tolerated treatment for migraine. Observed durations of benefit were consistent with known properties of BTX-A. Findings suggest that response may vary by features of preinjection headaches, such as migraine frequency. The precise mechanism by which BTX-A provides pain relief is hypothesized to be related not only to acetylcholine inhibition but also to a blocking action on the parasympathetic nervous system. Additional studies that control factors likely to be related to response may lead to better understanding of the BTX-A effect on migraine and an optimal treatment protocol.
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MIGRAINE, an episodic neurological disorder, affects about 17% of women and 6% of men in the US[1] and is a major stressor of the health-care providing system.[2,3] Disability from migraine is profound and disrupts functioning in the workplace and at home. Comorbidity of migraine with other major neurologic conditions has been established, including overlap with other major affective disorders (eg, panic disorder). There are numerous therapies currently available but most have limited benefit and can produce significant adverse side effects; thus, there is great demand for a long-acting acute and prophylactic therapy that is effective, well-tolerated, and lacks systemic side effects.[4]

Local injections of botulinum toxin type A (BTX-A; commercial preparation BOTOX, manufactured by Allergan Corporation, Irvine, CA) into excessive muscle contraction have been successful in treating dystonia, spasticity, and other conditions characterized by inappropriate muscle spasm.[5-10] When injected directly into contracting muscles, BTX-A exerts its effect by binding to the presynaptic nerve terminal, becoming internalized, and interfering with exocytosis of the neurotransmitter acetylcholine (Ach) at the neuromuscular juncture, thus inhibiting muscle contraction. Improvement in symptoms usually occurs within 1 to 14 days, peaks within 2 to 6 weeks, and begins to wear off by 10 to 12 weeks postinjection.[11] Functional recovery of the neuromuscular juncture takes about 3 to 6 months.[12] BTX-A is considered a safe therapy for inappropriate muscle spasms and is generally well tolerated, with adverse effects being typically self-limited. The greatest concern is probably the formation of blocking antibody leading to nonresponse of subsequent BTX-A injections. Prevalence of BTX-A resistence is less than 5%[13] and is likely associated with dose and frequency of treatment sessions but not by duration of overall treatment regimen.[11,14] However, most of these data are based on older batches of botulinum toxin that had greater amounts of protein load than the newer toxin, which has reportedly less antigenicity. Some of these patients have benefited from different preparations of BTX-A[15] or from other types of botulinum toxin.[16-19]

It has been observed by us and others that the therapeutic benefit of BTX-A can be isolated to pain relief alone.[20,21] One of the first pain syndromes for which BTX-A was successfully used was myofascial pain.[22,23] It has also been tested as a treatment for tension headache[24-28] and may be effective for cervicogenic headache[29] and chronic low back pain associated with muscle spasm.[30]

During initial clinical trials of BTX-A treatment for hyperfunctional facial lines, we observed that patients given pericranial BTX-A injections experienced relief of migraine headache symptoms.[31]

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This finding led to a multicenter, nonrandomized, open-label study to determine whether this relationship between BTX-A treatment and migraine symptoms was meaningful and could be replicated.[32] Double blind, placebo-controlled studies of BTX-A treatment for migraine followed.[33,34] This report details the findings of these studies (summarized in Table 1) and discusses the possible mechanisms by which BTX-A acts to relieve migraine symptoms.

OPEN-LABEL STUDY (BINDER)

A sample of study patients was recruited from private-practice cosmetic surgery, otolaryngology, and neurology clinics. Patients either a) sought BTX-A treatment for hyperfunctional facial lines or other dystonias with concomitant headache disorders or b) were candidates for BTX-A treatment specifically for headaches. Patients were classified as true migraine, possible migraine, or nonmigraine, based on baseline headache characteristics and International Headache Society (IHS) criteria.

The patients received prospective treatments either prophylactically or for acute migraine episodes; a small subgroup received both types of treatments. BTX-A injections were administered by experienced injectors[8,9] to the glabellar, temporal, frontal and, in 2 patients, the suboccipital regions of the head and neck. The injection protocol followed predetermined standards for the treatment of hyperfunctional facial lines and facial dystonias,[8] although those patients treated specifically for headache tended to receive larger doses as the study progressed. Patients had differing lengths of follow-up, ranging from 3 weeks to 6 months. Subsequent experience in treating migraine has now evolved into treatment patterns that incorporate the concept of injecting the areas of pain with larger doses varying between 75 to 125 U in multiple injection sites that "saturate" the area. The suboccipital region is routinely injected if pain is either referred or eminates from that area.

Treatment benefit was evaluated by self-reported degree and duration of response. Degree of response was defined as: a) complete response (elimination of headache symptoms), b) partial response (at least 50% reduction in frequency or severity of headaches) and c) nonresponse (less than 50% reduction in frequency or severity of headaches). Patients lost to follow-up were considered nonresponders.

Ninety-three patients received prophylactic treatment only, 4 received treatment for an acute migraine episode only, and 9 were treated for an acute episode and were subsequently treated prophylactically; the latter subgroup was included in both "prophylactic" and "acute" analyses. Seventy-nine (75%) patients were determined to have true migraine, 18 (17%) to have "possible" migraine, and 9 (9%) to have nonmigraine headaches. Most patients were women (90%), and the majority were 36 to 60 years old (68%). Fifty one percent of patients reported severe migraine symptoms, and 34% reported migraine frequency as 2 to 3 times per month. Nonmigraineurs were significantly more likely than possible or true migraineurs to report less severe headaches ($P = .03$). Gender, age, and baseline migraine frequency were similar among migraine classification groups, and neither baseline frequency nor severity varied by age or gender.

Seventy-seven true migraineurs were treated prophylactically; those with self-reported higher baseline migraine frequencies (at least 3 times/month) received higher doses than true migraineurs with lower baseline frequencies. Fifty one percent (95% CI = 39% to 62%) were complete responders with mean (standard deviation [SD]) duration of benefit of 4.1 (2.6) months. Complete response was related to lower baseline migraine frequency ($P = .06$) and severity ($P = .07$). However, "improvement" (complete or partial response) was unrelated to baseline frequency and severity. Overall, mean (SD) duration of benefit was 3.2 (2.3) months, independent of baseline frequency. Complete responders with severe baseline headaches had somewhat longer duration of benefit [mean (SD) = 4.6 (3.1) months] compared to those with less severe headaches at baseline [mean (SD) = 3.7 (2.3) months]. Although there was no evidence of dose-response (after adjustment for baseline frequency), injection site was a significant predictor of complete response ($P = .01$), with 87% of complete responders having received glabellar injections (compared to 66% of non- or partial responders). Complete responders were significantly older [mean (SD) age = 48 (12) years] than partial responders [mean (SD) = 43 (9) years] and nonresponders [mean (SD) = 41 (13) years] ($P = .02$).

Table 1. Details of 1 Open-Label and 2 Double-Blind Studies of BTX-A Treatment for Migraine

Study	Population	Sample	Treatment Protocol	Injection Sites	Follow-Up	Main Results
Open-label, Binder et al[32]	Patients seeking BTX-A treatment for hyperfunctional facial lines and/or dystonias with concomitant headache or specifically for headache.	106 patients, mostly women, 30-60 years old.	Prophylactic or acute injections per standards for hyperfunctional facial lines	Glabellar, frontal, temporal, suboccipital as indicated by headache characteristics.	Varied; ranged from 3 weeks to 6 months postinjections.	51% true migraine subjects treated prophylactically reported complete response with mean benefit duration = 4.1 months. Glabellar injections superior to other injection sites.
Double-blind, Silberstein et al[33]	Headache patients with histories of 2-8 moderate to severe migraines per month.	123 patients, mostly women, 22-63 years old.	Randomization to: 1) vehicle 2) 25 U BTX-A 3) 75 U BTX-A	Glabellar, frontal, temporal.	Monthly for 3 months postinjection.	25 U but not 75 U BTX-A superior to vehicle in reducing migraine frequency and severity, use of migraine medications, and vomiting.
Double-blind, Brin et al[34]	Headache patients with histories of 2-6 migraines per month.	53 patients, mostly women, 21-75 years old.	Randomization to: 1) frontal + temporal BTX-A 2) frontal BTX-A + temporal placebo 3) temporal BTX-A + frontal placebo 4) frontal + temporal placebo 45 U to frontal 30 U to temporal regions	Frontal, temporal.	2, 4, 8, 12, and 16 weeks postinjection.	Frontal + temporal BTX-A superior to placebo in reducing migraine severity at week 12 postinjection.

In the acute treatment experience, 10 of 13 true migraineurs were complete responders (70%; 95% CI = 35% to 93%). All responders improved within 1 to 2 hours postinjection.

There were no reported cases of true eyelid ptosis, diplopia, facial nerve or expression problems, keratopathy, or idiosyncratic or allergic reactions attributable to BTX-A treatment. Two patients reported transient brow ptosis; other adverse effects were limited to transient local pain and ecchymosis at the injection site.

DOUBLE-BLIND STUDY (SILBERSTEIN)

Eligible patients had histories of 2 to 8 moderate to severe IHS-defined migraines per month over the 3 months before enrollment and had 2 to 8 such migraines during a 1-month baseline period. Patients were recruited from 12 headache centers and were randomized to 1 of 3 groups: 1) Vehicle, 2) BTX-A, 25 U, or 3) BTX-A, 75 U. Symmetrical injections were administered to the frontal, temporal, and glabellar regions of the head. Follow-up data were collected at 3 monthly postinjection visits from diaries maintained by patients with the following parameters: the occurrence of migraines, start and stop times of migraines, severity of migraines, the presence of migraine aura, migraine-associated symptoms, and acute migraine medications used. The primary outcome in intent-to-treat analysis was change from baseline in number of moderate-to-severe migraines per month.

Forty-one patients were randomized to vehicle, 42 to 25-U BTX-A, and 40 to 75-U BTX-A. Most patients were women (85%). Age ranged from 22 to 63 years. Patients in the vehicle group were significantly older than those in the BTX-A groups ($P = .02$); all other demographic features were similar among groups. In migraine histories, mean frequencies/month were 4.8, 4.3, and 4.0 in the vehicle, 25-U BTX-A, and 75-U BTX-A groups, respectively; mean durations were 35.9, 32.9, and 32.2 hours, respectively. Treatment groups were comparable on migraine severity, distribution (unilateral versus bilateral), type of pain, or effect of physical activity. There were no significant differences by treatment group in baseline frequency of moderate-to-severe migraines, in maximum migraine severity, in migraine-associated vomiting, or in use of migraine medication. The vehicle and 25-U BTX-A groups had greater mean years since migraine onset ($P < .001$) and lower baseline frequencies of migraines of any severity ($p < 0.046$) than the 75-U BTX-A group; these variables were included as covariates in relevant analyses.

The 25-U BTX-A group experienced a significantly greater reduction in moderate to severe migraine frequency than the vehicle group at month 2 (-1.57 versus -0.37, $P = .008$) and at month 3 (-1.88 versus -0.98,$P = .04$) postinjection. Similarly, the 25-U BTX-A group experienced a significantly greater reduction in frequency of migraines of any severity than the vehicle group at month 3 (-2.12 versus -0.90, $P = .01$) and a tendency toward fewer migraines at month 2 (-1.55 versus -0.37, $P = .07$). At month 3, significantly more patients in the 25-U BTX-A group compared to the vehicle group reported at least 2 fewer migraines of any severity ($P = .01$) and a decrease in migraine frequency of at least 50% ($P = .046$).

Compared to vehicle, the 25-U BTX-A group experienced a significantly greater reduction in migraine severity at months 1 and 2 ($P < .03$) and in use of migraine medications at month 2 ($P = .03$). At month 3, significantly fewer patients in the 25-U BTX-A group experienced migraine-associated vomiting compared to vehicle ($P= .01$). Both drug groups had significantly better Subject Global Assessment scores than the vehicle group at month 2 (75-U BTX-A = 1.25, 25-U BTX-A = 1.19, vehicle = 0.46; $P< 0.041$).

The 75 U BTX-A group had higher incidence of treatment-related adverse events than the vehicle group (50% versus 24%, $P = .02$), whereas the 25-U BTX-A and vehicle groups were similar in adverse event incidence. All adverse events were transient and included blepharoptosis, diplopia, and injection site weakness.

DOUBLE-BLIND STUDY (BRIN)

Eligible patients had histories of 2 to 6 IHS-defined migraines per month over the 12 months prior to enrollment, including a 1-month baseline period. patients were recruited from 3 headache centers and were randomized to 1 of 4 injection groups:

1) BTX-A to the frontal and temporal regions; 2) BTX-A to the frontal region, placebo to the temporal region; 3) BTX-A to the temporal region, placebo to the frontal region; and 4) Placebo to the frontal and temporal regions. Forty five units (of

drug or placebo) were administered to frontal regions; 30 U were administered to temporal regions; thus, each patient received 75 U of drug and/or placebo. Sodium Chloride Injection, USP (normal saline with preservative [NS]) was used as the placebo. Follow-up data were collected at 2-, 4-, 8-, 12- and 16-week postinjection visits from diaries maintained by patients with the following parameters: the occurrence of migraines, start and stop times of migraines, severity of migraines, migraine-associated symptoms, and acute migraine medications used. Primary outcome measures in intent-to-treat analyses were frequency, duration, and pain intensity (0-10 scale) compared to baseline. Group 1 versus group 4 at week 12 was defined as the key comparison.

Fourteen patients were randomized to group 1, 12 to group 2, 14 to group 3, and 13 to group 4. Most patients were women (94%). Age ranged from 21 to 75 years. Patients in the placebo group were significantly older than those in the BTX-A groups ($P = .02$); all other demographic features were similar among groups. For migraines during the baseline period, the median maximum pain instensity was 10 (range, 0 to 10), the median frequency was 3.5/month (range, 0 to 9.7), and the median maximum duration was 25 hours (range, 0 to 130). The only significant difference in demographic and baseline characteristics by injection group was for migraine duration ($P = .04$); thus, baseline duration was used as a covariate in analyses of change in duration. Medication use was also controlled for as doing so appreciably affected results.

Maximum pain decrease for group 1 occurred by week 12 and was significantly greater than for group 4 [LS mean (se) = -4.3 (0.6) for group 1, -2.0 (0.6) for group 4; $P = .01$]. Groups 1 and 2 experienced greater decreases in migraine duration than groups 3 and 4 but these differences were not significant. Among patients with low (< 3.5/month) baseline migraine frequency, medication use over time significantly differed by treatment [$P = .0003$ for groups 1-3 (BTX-A) versus Group 4 (placebo)]; the largest difference was at week 12 ($P = .01$), and for BTX-A the decline in medication use over time was significant ($P = .007$). There were no discernable differences by treatment group in decrease of migraine frequency, vomiting, or number of nonmigraine days. Patients with frontal BTX-A injection sites had a marginally significantly greater reduction in pain at week 12 than other patients ($P = .054$).

DISCUSSION

The exact origin of migraine headache has yet to be determined but is hypothesized to involve vascular, neuronal, and myofascial components.[35-37] The trigeminoneurovascular theory suggests a viscious cycle in which pain sensation is transmitted to the central nervous system by afferent trigeminal neurons, activating the autonomic pathway through the facial nerve, and producing vasodilation because of involvement of the pterygopalatine and otic ganglia[38,39]; pain is then triggered via trigeminal neurons and the efferent parasympathetic pathway, producing feedback vasodilation. Vasodilation is thought to be mediated by the release of potent vasodilatory compounds, such as vasoactive intestinal peptide (VIP) and substance P from parasympathetic neurons innervating the pericranial vasculature. VIP has been identified at nerves associated with large cerebral arteries and extracranial vessels supplying the tongue, salivary gland, nose and eyes. In cats, it has been shown that VIP antibodies block the neurogenic vasodilatory response produced by electrical stimulation of the locus coeruleus or the pterygopalatine ganglion.[40] Release of vasoactive peptides, such as calcitonin gene-related peptide (CGRP), into the extracerebral circulation has been observed after activation of the trigeminovascular system and in patients experiencing migraine.[41]

The mechanism by which BTX-A provides pain relief in muscle contraction disorders is not known but has historically been thought to be related to the relief of muscle spasm through the inhibition of the release of Ach at the neuromuscular junction. If cranial muscle contraction is involved in migraine etiology, BTX-A would be expected to have a prophylactic effect. However, because BTX-A appears to provide both acute and chronic relief of migraine pain as well as other migraine-associated symptoms (eg, nausea and vomiting, visual disturbances, photophobia, and phonophobia), it seems likely that alternative mechanisms of action are at work. This is supported by the observation that BTX-A treatment of torticollis provides pain relief in excess of the reduction of inappropriate

muscle contraction, suggesting a different pathophysiological pathway than that related to muscle dysfunction.[20, 42]

BTX-A has been shown to block autonomic pathways, and other neuronal components and systems have different susceptibilities to botulinum toxin.[43] For example, parasympathetic postganglionic neurons that innervate canine submandibular glands are susceptible to the anticholinergic effect of botulinum toxin types A and D when applied topically to nasal mucosa.[44] These findings suggests that botulinum toxin, via injection or diffusion, affects important sites of action (possibly at the cellular level) other than the currently known neuroeffector sites. In addition, there is evidence that botulinum toxin has a direct effect on afferent fibers, suggesting that it also may block the sensory system.[45,46]

Botulinum toxins may inhibit the release of neurotransmitters and neuropeptides other than Ach.[47-53] Interestingly, both VIP and the vasoconstrictor neuropeptide Y were found to be colocalized with Ach in parasympathetic nerves originating in the sphenopalatine, otic, and internal carotid ganglia, all of which innervate cerebral arteries.[54] Also, evidence from immunohistological techniques suggests that botulinum toxin inhibits the release of CGRP from motor nerves in rats.[55]

These observations provide a potential link between the actions of botulinum toxin at cholinergic nerve terminals and its possible antivasodilatory and anti-inflammatory effects. After injection of BTX-A into muscles of the temple or forehead, it seems plausible that cholinergic (parasympathetic) neurons innervating the extracranial vasculature are recognized, causing a disruptive effect on the vesicular release of Ach and Ach-like neuropeptides. Because of the known cholinergic effect of BTX-A and the possible colocalization of vasodilatory neuropeptides, there is evidence to suggest that neurogenic inflammation, thought to play a role in migraine, resulting from the release of neuropeptides may be inhibited .

In the open-label and double-blind studies performed to date, summarized in this report, there is support for BTX-A as an efficacious, safe treatment for migraine, and the durations of benefit observed were consistent with known properties of BTX-A. However, these data also raise additional questions for further investigation. For example, all 3 studies suggest that response to treatment may vary depending on features of preinjection headaches. It would be of interest to determine which, if any, demographic, clinical, or other patient characteristics predispose to successful treatment response and are related to maximum effect. Also, the potential for placebo response to headache treatment has been documented,[56] and placebo effects were observed early in the course of follow-up in both double-blind studies. Therefore, a crossover study design to investigate the placebo effect might be worthwhile.

A study limited to BTX-A responders would be useful in optimizing doses, injection sites, and other treatment-related variables, as well as determining the specific effect of BTX-A on migraine symptoms. The two double-blind studies appear to have conflicting findings in terms of optimal dose: Silberstein et al found that 25 U BTX-A was superior to 75 U, and Brin et al. observed a treatment effect only for 75 U BTX-A (compared to 30 or 45 U).[33,34] In Brin et al, frontal BTX-A injection sites were associated with a somewhat greater reduction in pain than temporal BTX-A or placebo injections, whereas the open label study observed superiority for glabellar injections compared to other sites. Experience in treating migraine subsequent to these studies has resulted in a treatment concept of injecting the areas of pain with larger doses varying between 75 to 125 U in multiple injection sites that "saturate" the area. The suboccipital region is routinely injected if pain is either referred or eminates from that area. In terms of specific BTX-A effects, Silberstein et al found an association between BTX-A and reduction of migraine frequency, severity, use of medications, and vomiting; Brin et al. observed a reduction in severity and, in patients with less frequent migraines at baseline, in medication use. Better control of factors likely to be related to treatment response through study design may be helpful in gaining better understanding of the effect of BTX-A on migraine and its optimal method of delivery.

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