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A Series of Three Sequential, Randomized, Controlled Studies of Repeated Treatments With Botulinum Toxin Type A for Migraine Prophylaxis

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Abstract: We examined the effects of multiple treatments with low doses of botulinum toxin type A (BoNTA; BOTOX®, Allergan Inc., Irvine, CA) versus placebo for prophylaxis of episodic migraine. This was a series of 3 sequential, randomized, controlled studies of 418 patients with a history of 4 to 8 moderate to severe migraines per month. In study I, patients were randomized to treatment with placebo or BoNTA (7.5 U, 25 U, or 50 U) in predetermined fixed injection sites on the front and sides of the head only. In study II, patients continued to receive, or were randomized to, 2 consecutive treatments with 25 U or 50 U. In study III, patients were randomized to placebo or continuation of 25 U or 50 U. Injection cycles were each 4 months long. BoNTA and placebo produced comparable decreases from baseline in the frequency of migraines at each time point examined ($P \geq .201$). No consistent, statistically significant differences were observed for any efficacy variable. Adverse events were similar among the groups within each study. In these exploratory studies of episodic migraine patients, repeated injections of low doses of BoNTA into fixed frontal, temporal, and glabellar sites were not more effective than placebo. BoNTA was safe and well tolerated.

***Perspective:** Beneficial effects of BoNTA in the treatment of migraine have been reported, but positive results are not universal, possibly because the optimal patient population and regimen are not yet definitively established. This study explores the effects of multiple injections of low BoNTA doses into fixed sites for episodic migraine.*

***Key words:** Episodic migraine, botulinum toxin type A, headache, injection, BOTOX.*

Migraines can often be treated effectively with abortive medications such as the triptans or non-steroidal anti-inflammatory drugs. However, a substantial number of patients do not respond to abortive treatments and, in many cases, individuals who experience 3 or more migraine attacks per month require prophylactic treatment. The available medications frequently prescribed for migraine prophylaxis include antiepileptics such as divalproex sodium and topiramate,[22,30] as well as beta blockers such as propanolol.[17] However, the use of these medications is considerably limited by systemic adverse effects such as weight gain, asthenia, paresthesias, diarrhea, vomiting, and somnolence, as well as modest therapeutic benefits in some cases.[14,22,30]

Botulinum toxin type A (BoNTA) is an injectable protein complex that has been used since the early 1980s for

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the treatment of selected ophthalmic conditions;[27] its use has expanded to numerous conditions and approval has been granted in the U.S. and/or Europe for a number of conditions, including blepharospasm, cervical dystonia, glabellar lines, hyperhidrosis, strabismus, poststroke upper-limb spasticity, and juvenile cerebral palsy. The ability of BoNTA to reduce pain was first reported in patients with cervical dystonia,[33] a movement disorder characterized by painful contractions of the neck and shoulder muscles that pull the head away from its normal resting position. The beneficial effects of BoNTA for the treatment of chronic headaches not associated with dystonia were reported as early as 1994,[1,10] with subsequent studies reporting benefits in episodic migraine.[29]

It is generally agreed that the traditional mechanism of action described for BoNTA, inhibition of acetylcholine release, cannot explain its purported effects in migraine or several other disorders in which pain is a primary component.[8] In preclinical studies, BoNTA has been found to inhibit the release of substance P from cultured dorsal root ganglia neurons.[26,37] Additionally, BoNTA has been found to inhibit the release of calcitonin gene-related peptide from cultured rat trigeminal neurons.[12] It has been proposed that the ability of BoNTA to inhibit these inflammatory mediators may contribute to its effects on pain in preclinical models and in clinical conditions such as migraine.[3,12,32]

Despite this preclinical evidence, results with BoNTA in episodic migraine trials have been inconsistent.[15] This has led to controversy about the efficacy of BoNTA for episodic migraine.[15] We have conducted a series of 3 sequential, randomized, controlled trials designed to further explore the effects of BoNTA for episodic migraine prophylaxis. In the first study, a low dose of BoNTA (7.5 U) was included as an active control to counter the possibility that patients might discern their assignment to active drug based on the sensation of facial muscle weakening and/or an improved appearance of facial lines. Repeated treatments were included to determine whether results were superior to a single treatment. A withdrawal phase was introduced as the third study in this series, in which half of the remaining patients were randomized to placebo after receiving 2 or 3 consecutive BoNTA treatments. It was reasoned that the novel effects of the injection procedures and any other factors responsible for an initial placebo effect may stabilize over repeated injections. In this case, a treatment effect may emerge once patients had habituated to the injections, which would be evident as a worsening of symptoms in the group randomized to placebo.

Table 1. Injection Sites and Doses

	Total Units (U) and Total Volume (mL) Injected per Muscle Area			
Treatment Group	Frontal (4 sites)	Temporal (2 sites)	Glabellar (5 sites)	Total Dose
High dose	20 U 0.60 mL	12 U 0.36 mL	18 U 0.54 mL	50 U 1.5 mL
Medium dose	10 U 0.60 mL	6 U 0.36 mL	9 U 0.54 mL	25 U 1.5 mL
Low dose	3 U 0.60 mL	1.8 U 0.36 mL	2.7 U 0.54 mL	7.5 U 1.5 mL
Placebo	0 U 0.60 mL	0 U 0.36 mL	0 U 0.54 mL	0 U 1.5 mL

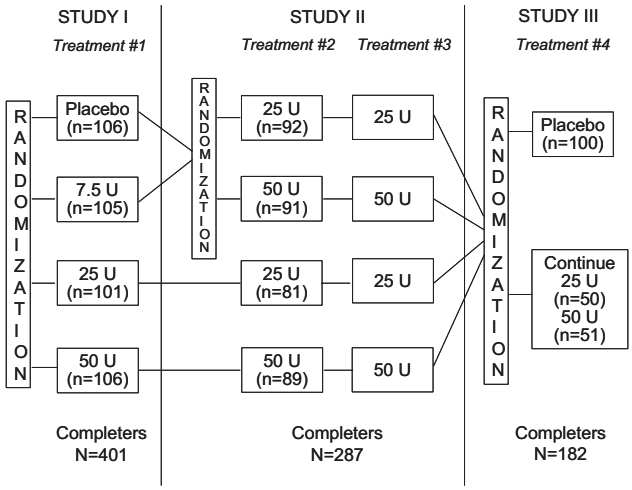

Figure 1. Study design and patient disposition. Patients were followed up every 30 days for 120 after each treatment, except for the last treatment (#4), after which patients were followed for 180 days. Discontinuations in study I: n = 6 (placebo), n = 3 (50 U), n = 6 (25 U), n = 2 (7.5 U); discontinuations in study II: n = 16 (50 U/50 U), n = 7 (7.5 U/50 U), n = 13 (0 U/50 U), n = 15 (25 U/25 U), n = 8 (7.5 U/25 U), n = 7 (0 U/25 U); discontinuations in study III: n = 3 (50 U/50 U), n = 7 (25 U/25 U), n = 4 (50 U/0 U), n = 5 (25 U/0 U).

Materials and Methods

Study Design and Patients

This was a series of 3 sequential studies that were multicenter, randomized, and double-blind. In study I, patients were randomized to treatment with placebo or BoNTA injected into frontal, glabellar, and temporal muscle areas only for a total dose of 7.5 U, 25 U, or 50 U (Table 1; Fig 1). Patients who completed this study could then enter study II, in which those who had received placebo or the low dose of BoNTA (7.5 U) were randomized within treatment group to receive 2 treatments of either 25 U or 50 U BoNTA. Patients who had received BoNTA-25 U or BoNTA-50 U in the previous study were to continue receiving the same doses for 2 additional treatments. Patients who completed this second study could then enter study III, in which they were randomized within treatment group to a treatment with placebo or to continued treatment with 25 U or 50 U. All treatments across the 3 studies were administered at 4-month intervals. Dosing and results reported in this study are specific to the formulation of botulinum toxin type A manufactured by Allergan, Inc. (Irvine, CA). The Allergan, Inc., formulation is not interchangeable with other botulinum toxin products and cannot be converted by using a dose ratio.

Patients included both males and females, 18 to 65 years of age, with International Headache Society–defined migraines with or without aura. Eligible patients were to have