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ScienceDirect

Journal of the Chinese Medical Association 77 (2014) 10–15

www.jcma-online.com

Original Article

Efficacy, safety, and predictors of response to botulinum toxin type A in refractory chronic migraine: A retrospective study

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Received January 10, 2013; accepted April 16, 2013

Abstract

Background: Due to its persistent and debilitating nature, refractory chronic migraine (RCM) can cause significant socioeconomic burden. This study retrospectively reviewed the efficacy and safety of botulinum toxin type A (BoNT-A) in the treatment of RCM. Predictors of treatment response were also investigated.

Methods: We enrolled 94 patients in this study after reviewing the records of those patients who received BoNT-A injections ≥75 U in our headache clinic, and who fulfilled the criteria for RCM established by Schulman et al. The outcome variables included headache frequency, migraine disability assessment score, and adverse events recorded in headache diaries. Treatment response was defined as ≥30% reduction in headache frequency from baseline at 12 weeks. Potential predictors of treatment response were evaluated, including patient demographics, headache directionality, ocular-type headache, medication overuse, BoNT-A dosage, body mass index, and Beck depression inventory score.

Results: For the 94 patients with RCM who were enrolled, their mean baseline headache frequency was 23.9 days/28 days. At 12 weeks after BoNT-A injection, the mean reduction in headache frequency was 6.5 days/28 days ($p < 0.001$), and the median migraine disability assessment score decreased from 60.0 to 30.0 ($p < 0.001$). Thirty-seven (39.4%) patients responded to treatment, and only ocular-type headache was associated with a higher response rate (ocular vs. nonocular, 54.8% vs. 31.7%; $p = 0.031$). The most common adverse event was lateral eyebrow elevation (19.1%), followed by neck soreness (5.3%).

Conclusion: About 40% of patients with RCM obtained ≥30% reduction in headache frequency at 12 weeks after BoNT-A injection, and treatment-related adverse events were transient and acceptable. Ocular-type headache may predict treatment response.

Keywords: botulinum toxin type A; refractory chronic migraine; treatment

1. Introduction

Chronic migraine (CM) is a disabling headache disorder affecting 1.4–2.2% of the general population,[1–3] causing significant disability and negatively impacting quality of life.[3–6] It is recognized as a complication of migraine in the International Classification of Headache Disorders, 2nd Edition (ICHD-2),[7] and subsequent revised criteria (ICHD-2R) for CM specify that affected patients have headaches on ≥15 days/month for ≥3 months, with headaches occurring on ≥8 days classified as migraines, or responsive to migraine-specific medications.[7,8] Patients with CM generally have unsatisfactory responses to abortive or preventative treatments;[3,9] headaches fail to respond to any adequate pharmaceutical intervention in a subset of these patients, who are classified as having refractory CM (RCM). This condition

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1726-4901/$ - see front matter
http://dx.doi.org/10.1016/j.jcma.2013.09.006

is now well-documented[10,11] and Schulman et al.[12,13] proposed diagnostic criteria (Table 1). RCM causes more significant disability and socioeconomic burdens than CM, and the development of an effective treatment for patients with this condition is crucial.

Recently, botulinum toxin type A (BoNT-A) and topiramate have been proven to be beneficial for CM prophylaxis,[14−17] but their efficacy for RCM needs to be examined. In addition to evaluating the effectiveness and safety of BoNT-A injection in patients with RCM, this study also aimed to investigate possible predictors of treatment response.

2. Methods

2.1. Clinical setting

Taipei Veterans General Hospital is a 3015-bed tertiary medical center serving veterans and nonveteran citizens, and the hospital's headache clinic has been operating since 1997. Taiwan's National Health Insurance (NHI) Program was launched in 1995 and covered >99% of the population in 2008. Patients can choose to visit any hospital or physician, regardless of illness severity.

When visiting our headache clinic, all patients completed a structured headache questionnaire and were instructed to keep a headache diary in order to obtain accurate headache information and evaluate treatment response. Patients with CM were given the option of BoNT-A injection, and the decision to undergo this treatment depended on each patient's willingness and the ability to cover treatment costs. Because BoNT-A is not covered by the NHI in Taiwan and the price is high (>20-fold higher than a regular clinic visit), patients tended to select BoNT-A injection only when their headaches were refractory to all oral medications. A written informed consent for BoNT-A injection was obtained from each patient prior to the injection because this medication was not indicated for treatment of chronic migraine.

This retrospective review was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (Taipei, Taiwan).

Table 1
Proposed criteria for refractory chronic migraine.

1. Patient has diagnosis of chronic migraine (or migraine)
2. Patient has failed adequate trial of at least two of the following four drug classes
   A. Anticonvulsants
   B. Beta blockers
   C. Tricyclics
   D. Calcium channel blockers
3. Patient has modified lifestyle and eliminated triggers
4. Patient has failed abortive medications, including
   A. Triptans and DHE
   B. NSAIDs and combination analgesics
5. Modifiers may be present:
   A. With or without medication overuse
   B. With significant disability

DHE = dihydroergotamine; NSAIDs = nonsteroidal anti-inflammatory drugs.

2.2. Patients

The medical records, headache questionnaires, and diaries were retrospectively reviewed of patients who were diagnosed with RCM based on the criteria proposed by Schulman et al[12,13] (Table 1) and who had received BoNT-A treatment (BOTOX; Allergan Inc., Irvine, CA, USA) between June 2008 and April 2012.

Of note, the available abortive medications for migraine in Taiwan are oral dihydroergotamine (DHE) and oral or intranasal triptans; other formulations of triptan and parenteral DHE, the use of which is proposed in the criteria for RCM, are not available.

2.3. Treatment paradigm

BoNT-A was administered to our patients in 21 or 31 fixed-site, fixed-dose (FSFD) injections. Patients received either single injection or a series of injections depending on their ability and wishes. The protocol used from June 2008 to July 2010 was 100 U or 75 U BoNT-A at 21 sites, whereas the FSFD protocol used from August 2010 (155 U BoNT-A at 31 sites) followed the injection paradigm of the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) studies.[16−18] In both treatment paradigms, BoNT-A was administered across several head and neck muscles. All patients received FSFD injections at two corrugator, one procerus, four frontalis, eight temporalis, and six occipitalis sites; those for whom the PREEMPT paradigm was followed received additional injections at four cervical paraspinal and six trapezius sites.[16−18] The concurrent use of headache preventive medications and/or acute abortive treatment was not prohibited during the BoNT-A injection treatment period.

2.4. Clinical information

Patients' medical records, headache questionnaires, and headache diaries were analyzed to obtain information about demographics, Beck depression inventory (BDI) scores,[19] body mass index (BMI),[20] and headache profiles including CM duration, concurrent use of headache preventive medications, overuse of abortive medications (MO), headache directionality, ocular-type headache, adverse events (AEs), injection dosage, headache frequency, and migraine disability assessment score (MIDAS).[21,22]

Headache diaries maintained by patients within 28 days prior to BoNT-A injection were used as a baseline. At baseline, if the patients took abortive medication such as analgesics and nonsteroidal anti-inflammatory drugs for 15 days/month, and mixed drugs (triptans, ergotamines, opioids, and nonsteroidal anti-inflammatory drugs) for 10 days/month, they were classified as patients with MO.[23] The injection day was labeled Day 0, and changes in headache frequency and MIDAS at 12 weeks were calculated. Headache frequency was defined as a calendar day when the patient reported ≥4 continuous hours of headache diary episode. The MIDAS was used to assess headache-related disabilities, classified using

four disability grades: Grade I, total score 0–5, indicating minimal or infrequent disability; Grade II, total score 6–10, mild or infrequent disability; Grade III, total score 11–20, moderate disability; and Grade IV, total score ≥21, severe disability.[22,24] Patients with ≥30% reduction in headache frequency from baseline at 12 weeks were categorized as responders, and other patients were classified as nonresponders.

Patients' demographics, BDI score, BMI, and some headache profiles including MO,[25] injection dosage, headache directionality[26,27] (see below), and ocular-type headache were used to predict treatment response. In contrast to other studies,[26,27] our classification of headache directionality included only imploding, exploding, and equal-type headaches; the presence or absence of ocular-type headache was further discriminated in our patients from headache directionality.

To determine headache directionality, we asked patients to report whether their headaches were predominantly imploding or exploding.[26,27] An exploding headache was described as a buildup of pressure inside the head, and an imploding headache was described as the sensation of the head being crushed, clamped, or stubbed by external forces.[26] Patients with similar frequencies of imploding and exploding headaches were assigned to the equal-type headache group. Patients were also classified according to the occurrence of ocular-type headache by reporting whether they experienced eye-popping pain during ≥50% of headaches (ocular-type group); patients who experienced such pain during <50% of headaches were assigned to the non–ocular-type group.

2.5. Statistical analysis

Statistical analyses were performed using SPSS software (PASW, version 18.0 for Windows; SPSS Inc., Chicago, IL, USA). Paired and Student *t* tests were used to compare continuous data with normal distributions in two related and independent groups, respectively. The Mann–Whitney *U* test was used for continuous data without normal distributions. The Chi-square test or Fisher's exact test was used for categorical data. The McNemar test was used to evaluate changes in paired binominal attributes. A two-sided test with $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Participants

The records of 110 patients with RCM who received BoNT-A injections during the study period were reviewed. A total of 16 patients were excluded due to incomplete headache questionnaires ($n = 9$) or administration of <75 U BoNT-A ($n = 7$). Ninety-four patients (15 men, 79 women; mean age, 47.6 ± 13.6 years) were thus included in the analyses. The average CM duration was 8.1 ± 8.2 years, the mean BDI score was 15.0, and the mean BMI was 23.5. About 20% of patients showed MO while receiving BoNT-A injection treatment (Table 2). The distributions of headache directionality and ocular-type headache are listed in Table 2. The initial protocol (100 U or 75 U at 21 sites; 100 U, $n = 59$; 75 U, $n = 8$) was used for 67 (71.3%) patients, and the PREEMPT FSFD paradigm (155 U at 31 sites) was used for 27 (28.7%) patients.

Table 2
Patient demographics and headache profiles.

	Total ($n = 94$)	Range
General		
Female	79 (84.0)	—
Age (y)	47.6 ± 13.6	20–85
CM duration (y)	8.1 ± 8.3	1–40
BDI score	15.0 ± 9.4	0–38
BMI (kg/m^2)	23.5 ± 4.1	15.1–36.5
Medication overuse	18 (19.1)	—
Headache characteristics		
Baseline headache frequency (d/28 d)	23.9 ± 8.1	8–30
Baseline MIDAS (median)	60.0	0–270
Headache directionality		
Exploding	50 (53.2)	—
Imploding	25 (26.6)	—
Equal	19 (20.2)	—
Ocular-type headache	31 (33.0)	—
Number of preventive agents used at baseline		
Single preventive agent	20 (21.3)	—
Two preventive agents	48 (51.0)	—
Three preventive agents	22 (23.4)	—
Four preventive agents	4 (4.3)	—

Data are presented as *n* (%) or mean ± SD, unless otherwise indicated.
CM = chronic migraine; BDI = beck depression inventory; BMI = body mass index; MIDAS = migraine disability assessment score, Taiwanese version.

Four kinds of prophylactic agents were mainly used in our patients on Day 0, including β-blocker (propranolol), calcium channel blocker (flunarizine), antiepileptics (topiramate, valproate) and antidepressants (amitriptyline, venlafaxine, duloxetine). Most patients received combination therapy, and the frequencies of different combinations were: single (21.3%), two (51.0%), three (23.4%), and four preventive agents (4.3%; Table 2).

3.2. Clinical profiles

The baseline headache frequency was 23.9 ± 8.1 days/28 days. At 12 weeks, the frequency of headaches decreased to 17.4 ± 11.0 days/28 days, representing a mean reduction from baseline of 6.5 ± 8.9 days ($p < 0.001$).

The median MIDAS prior to injection was 60.0 (range, 0–270), with 19.1% of patients classified as Grade I (score 0–5), 4.3% each as Grade II (score 6–10) and Grade III (score 11–20), and 72.3% classified as Grade IV (score ≥21). At 12 weeks, the median MIDAS was 30.0 (range, 0–270) with 26.6% of patients classified as Grade I, 10.6% as Grade II, 7.4% as Grade III, and 55.3% as Grade IV. The improvement in the median MIDAS was significant (baseline vs. 12 weeks, 60.0 vs. 30.0; $p < 0.001$).

3.3. Predictors of treatment response

Among 94 enrolled patients, 37 (39.4%) fit the criteria of responders at 12 weeks after BoNT-A injection. The

responders had a higher frequency of ≥50% improvement of MIDAS than the nonresponders (Table 3). However, no further association was noted between responders and the different combinations of preventive agents (Table 3). Thirty-one (33.0%) patients had ocular-type headache (Table 2). Compared with the nonocular type, patients with ocular-type headache were more likely to be responders (ocular vs. nonocular, 54.8% vs. 31.7%; $p = 0.03$; Table 3). However, the mean reduction headache frequency did not differ significantly between patients with and without ocular-type headache (8.8 ± 8.9 days and 5.5 ± 8.4 days/28 days, $p = 0.089$).

Headache directionality was not associated with treatment response (Table 3). We also found no association between treatment response and demographic or headache profile variables, such as age, sex, MO, BDI score, or BMI ≥25 kg/m^2. Furthermore, BoNT-A dosage was not associated significantly with treatment response, although the response rate was lowest in patients receiving 75-U BoNT-A injections (155 U vs. 100 U vs. 75 U, 44.4% vs. 40.7% vs. 12.5%; $p = 0.280$; Table 3).

3.4. Adverse events

There were 27 (28.7%) patients reported AEs (Table 4). The most common AE was lateral eyebrow elevation (18 patients, 19.1%), followed by neck soreness (5 patients, 5.3%) and ptosis (4 patients, 4.3%). The occurrence of AEs did not differ significantly according to injection dosage (155 U vs. 100 U vs. 75 U, 33.3% vs. 28.8% vs. 12.5%; $p = 0.564$). It was observed that AEs resolved spontaneously within 1–2 months (49.5 ± 18.5 days) with no sequelae.

Table 3
Demographics and treatment and headaches profiles of responders and nonresponders.

	Total ($n = 94$)		p
	Responders ($n = 37$)	Nonresponders ($n = 57$)	
Mean age (y)	47.6 ± 12.9	47.6 ± 14.1	0.992
Female	29 (78.4)	50 (87.7)	0.227
Medication overuse	7 (18.9)	11 (19.3)	0.964
BDI score	14.7 ± 8.9	15.2 ± 9.7	0.931
BMI ≥25	7 (18.9)	20 (35.1)	0.091
≥50% reduction of MIDAS	25 (67.6)	11 (19.3)	<0.001*
Number of preventive agents			0.289
Single preventive agent ($n = 20$)	11 (29.7)	9 (15.8)	
Two preventive agents ($n = 48$)	15 (40.6)	33 (57.9)	
Three preventive agents ($n = 22$)	9 (24.3)	13 (22.8)	
Four preventive agents ($n = 4$)	2 (5.4)	2 (3.5)	
BoNT-A dosage			0.280
155 U ($n = 27$)	12 (44.4)	15 (55.6)	
100 U ($n = 59$)	24 (40.7)	35 (59.3)	
75 U ($n = 8$)	1 (12.5)	7 (87.5)	
Headache directionality			0.127
Exploding ($n = 50$)	19 (38)	31 (62)	
Imploding ($n = 25$)	7 (28)	18 (72)	
Equal ($n = 19$)	11 (57.9)	8 (42.1)	
Ocular-type headache			0.031*
Yes ($n = 31$)	17 (54.8)	14 (45.2)	
No ($n = 63$)	20 (31.7)	43 (68.3)	

Data are presented as n (%).
*$p < 0.05$.
BDI = Beck Depression Inventory; BMI = body mass index; BoNT-A = botulinum toxin type A; MIDAS = migraine disability assessment score.

Table 4
Adverse events according to botulinum toxin type A injection dosage.

	155 U $n = 27$	100 U $n = 59$	75 U $n = 8$	Total $n = 94$
All adverse effects	9 (33.3)	17 (28.8)	1 (12.5)	27 (28.7)
Lateral eyebrow elevation	7 (25.9)	11 (18.6)	0 (0)	18 (19.1)
Neck soreness	2 (7.4)	3 (5.1)	0 (0)	5 (5.3)
Ptosis	0 (0)	3 (5.1)	1 (12.5)	4 (4.3)

Data are presented as n (%).

4. Discussion

Among 94 patients with RCM enrolled in our study, about 40% experienced ≥30% reduction in headache frequency, with an average decrease of 6.5 headache days/28 days at 12 weeks. The median MIDAS also improved after treatment. Patients with ocular-type headache showed a trend of greater reduction in headache days than did those without such headaches. The AEs were acceptable and self-limited.

Unlike most patients with CM who do not receive adequate treatment,[3] patients with RCM are defined as refractory to at least 2-month regimens of optimal doses of preventive medication and abortive treatment.[12] On receiving BoNT-A injection, 78.7% of our patients were on two or more kinds of preventive agents. Despite adequate preventive treatment, headache frequency remained high (23.9 days/28 days) in patients in our study and 76.6% had MIDAS >10. These factors indicate that our patients were highly disabled, regardless of adequate preventive medication regimens. Hence, this study provided a clinical observation of the prophylactic efficacy of BoNT-A injection for RCM.

Our study differs from the PREEMPT studies in several ways. First, our patients fulfilled the criteria of RCM, rather than only CM. Second, our patients were still on preventive medications when receiving BoNT-A injection.[16,17] Third, our study had a retrospective open-label design, rather than being a randomized control trial. Fourth, we used a primary outcome timepoint of 12 weeks, rather than the 24 weeks used in the PREEMPT studies. In the PREEMPT studies, reductions in headache frequency from baseline were 8.4 days/28 days at 24 weeks and around 7.4 days at 12 weeks.[28,29] The mean headache frequency prior to treatment was higher in our study than in the PREEMPT studies (23.9 vs.19.9 days/28 days), but slightly less reduction in headache frequency was observed at 12 weeks after treatment (6.5 vs. 7.4 headache days/28 days).[28,29]

The incidence rates of AEs in our patients were similar to those reported in the PREEMPT studies[28] (all AEs, 28.7% vs. 29.4%; Table 4), and were not associated with injection dosage. The PREEMPT studies reported eyelid ptosis in 3.6% of patients receiving a total dose of 35 U BoNT-A to the frontalis, corrugator, and procerus muscles,[28] compared with an incidence rate of 4.3% in our study in patients receiving

similar BoNT-A doses (26−35 U) to these three muscles. Of note, the frequency of lateral eyebrow elevation in our study (19.1%) was relatively high among all AEs. Most AEs were transient and subsided within 1−2 months. Overall, the AEs observed in our study were acceptable, and we report no new safety finding that would affect the known tolerability profile of BoNT-A.[28,30,31]

Traditionally, central hypersensitivity is thought to play an important role in CM.[32] The mechanism of BoNT-A for CM prophylaxis is proposed to involve the inhibition of peripheral trigeminal sensory fiber sensitization, which in turn modulates the activity of central trigeminal neurons and thus indirectly leads to the inhibition of migraine headache.[33,34] RCM may have the same pathophysiology as CM, but further investigation is necessary to resolve this issue. Previous studies found that some headache characteristics, such as ocular type, imploding directionality, and aura, predicted the response to BoNT-A injection.[26,27,35] However, not all patients enrolled in those studies had CM, and the findings might not be generalizable to patients with CM. For patients with RCM, our study showed that only ocular-type headache was associated with a higher response rate to BoNT-A. Other predictors of treatment response, such as headache directionality, MO, BDI score, age, sex, injection dosage, and BMI $\geq$25, had no significant association with treatment response (Table 3). Of note, the small number of patients receiving 75-U BoNT-A injections might have increased the risk of false-negative findings when analyzing the relationship between injection dosage and response. In fact, the response rate was nominally lower in these patients than in those receiving higher doses (155 U vs. 100 U vs. 75 U, 44.4% vs. 40.7% vs. 12.5%). This finding corresponded with those of previous studies that $\geq$100 U BoNT-A is more likely to be effective for migraine prophylaxis.[18,36]

Our study had several limitations. First, it was a retrospective chart review including patients treated with different BoNT-A injection paradigms, and no placebo group was included for comparison. Second, we used the modified RCM criteria[12,13] because intranasal or injectable DHE and injectable triptans are not available in Taiwan. Third, the measurement of headache directionality used in our headache questionnaire was not completely the same as used in previous studies, and we should be cautious to extrapolate our study results when compared to other studies. Fourth, a large proportion of patients with RCM sought adjunctive therapies such as Chinese herbs or acupuncture prior to receiving BoNT-A injection, because the current NHI system in Taiwan does not cover the costs of BoNT-A injection treatment. This sociodemographic issue may alter patients' willingness to receive BoNT-A injection, and may have caused selection bias in our study. Hence, additional studies comparing the cost effectiveness of BoNT-A and other treatment modalities are needed, including consideration of the cost of healthcare resource utilization, health-related quality of life, and loss of productivity, especially in patients with RCM.

In conclusion, about 40% of patients with RCM achieved 30% reduction in headache frequency at 12 weeks after BoNT-A injection. AEs were generally acceptable. Additionally, patients with ocular-type headache were more likely to respond to this treatment.

Acknowledgments

This study was supported in part by grants from Taiwan National Science Council (100-2314-B-010-019-MY2, 100-2314-B-010-018-MY3), Taipei Veterans General Hospital (VGHUST101-G7-1-1, V101C-106, V101E7-003, V99B1-002), NSC support for the Center for Dynamical Biomarkers and Translational Medicine, National Central University, Taiwan (NSC100-2911-I-008-001), Brain Research Center, National Yang-Ming University, and a grant from Ministry of Education, Aim for the Top University Plan.

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