
Research Submission

A Multi-Center Double-Blind Pilot Comparison of OnabotulinumtoxinA and Topiramate for the Prophylactic Treatment of Chronic Migraine

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Objective.—This multi-center pilot study compared the efficacy of onabotulinumtoxinA with topiramate (a Food and Drug Administration approved and widely accepted treatment for prevention of migraine) in individuals with chronic migraine (CM).

Methods.—A total of 59 subjects with CM were randomly assigned to one of 2 groups: Group 1 (n = 30) received topiramate plus placebo injections, Group 2 (n = 29) received onabotulinumtoxinA injections plus placebo tablets. Subjects maintained daily headache diaries over a 4-week baseline period and a 12-week active study period. The primary endpoint was the Physician Global Assessment, which measured the treatment responder rate and indicated improvement in both groups over 12 weeks. Secondary endpoints, measured at weeks 4 and 12, included headache days per month, migraine days, headache-free days, days on acute medication, severity of headache episodes, Migraine Impact & Disability Assessment, Headache Impact Test, effectiveness of and satisfaction with current treatment on the amount of medication needed, and the frequency and severity of migraine symptoms. At 12 weeks subjects were re-evaluated and tapered off oral study medications over a 2-week time period. Subjects not reporting a >50% reduction of headache frequency at 12 weeks were invited to participate in a 12-week open label extension study with onabotulinumtoxinA. Of these, 20 subjects, 9 from the Topiramate Group and 11 from the OnabotulinumtoxinA Group, volunteered for this extension from weeks 14 to 26.

Results.—This study demonstrated positive benefit for both onabotulinumtoxinA and topiramate in subjects with CM. Overall, the results were statistically significant within groups but not between groups. By week 26, subjects had a reduction of headache days per month compared with baseline. This was a significant within-group finding.

Conclusion.—OnabotulinumtoxinA and topiramate demonstrated similar efficacy for subjects with CM as determined by Global Physician Assessment and supported by multiple secondary endpoint measures.

Key words: onabotulinumtoxinA, topiramate, migraine prophylaxis, chronic migraine, physician global assessment

Abbreviations: HIT-6 Headache Impact Test, MIDAS Migraine Impact & Disability Assessment, MIQ Migraine Impact Questionnaire

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INTRODUCTION

Historically migraine has been considered an episodic pain syndrome.¹ As such, treatment has largely focused on terminating or ameliorating symptoms associated with the acute event of migraine. To this point during the 1980s and 1990s the Food and Drug Administration (FDA) approved 9 drugs for acute treatment of migraine but only divalproate sodium was approved for migraine prevention.² As an understanding of the chronic nature of migraine has evolved, the importance of preventive therapy has become increasingly evident.³ Consequently, there have been several clinical trials of preventive therapy for migraine within the last decade, which has led to FDA approval of a second anti-epileptic medication (AED) for the prevention of migraine, topiramate in 2003.⁴ Curiously other AED medications failed to demonstrate efficacy in preventing migraine despite presumed advances in understanding migraine pathophysiology.^{5,6} Whether this reflects limitations in our scientific understanding of the biology of migraine prevention, or the methodological limitations in designing successful and meaningful clinical trials of pharmacological agents for migraine prevention or both, is a matter of debate.

OnabotulinumtoxinA (botulinum toxin type A) was first reported to prevent migraine by Binder in 1991.⁷ Since that time, numerous clinical trials have been conducted with onabotulinumtoxinA yielding mixed results.⁸ The American Association of Neurology published a consensus paper in 2008 suggesting that onabotulinumtoxinA was ineffective as a migraine preventive for episodic migraine and inconclusive for chronic migraine (CM).⁹ Since then, Dodick, Aurora, and Diener reported that in 2 large separate parallel studies on subjects with CM, statistically significant efficacy for onabotulinumtoxinA over placebo.¹⁰⁻¹² Ensuing debate has challenged whether the findings of this study are truly clinically relevant although a statistical measure of meaningful clinical relevance has yet been defined. More recently, onabotulinumtoxinA has been licensed by the Medicine and Healthcare Products Regulatory Agency in the UK for the prophylaxis of headaches in adults who have CM.¹³ This may suggest that the debate over the migraine preventive

potential of onabotulinumtoxinA in CM is becoming less ambiguous.

The study presented here is designed to approximate clinical decision making and assimilation of risks and benefits that clinicians use to assess migraine preventive medication in the “real world” clinical care of migraine patients. The primary endpoint in this study is a Global Physician Assessment based on interviews and diary analyses between investigator and subject. The authors believe that this methodology permits a more integrated and relevant evaluation of efficacy than simply a *P* value of pre-specified endpoints. Historically endpoints, such as the number of migraine episodes or headache days in a specified time period, have stood as the gold standard for success of migraine preventive therapy yet interestingly evidence for these endpoints being clinically meaningful are largely based on consensus. To this end, the study presented is an effort to help augment and clarify what has been a murky and often inconclusive exploration of onabotulinumtoxinA in the prevention of migraine.

METHODS

Study Design.—This was a 3-center, double-blind randomized pilot study of onabotulinumtoxinA and topiramate for preventive treatment of CM defined as 3-8 attacks of migraine per month with on average 21 days of headache per month.

The study was conducted in compliance with investigational review board regulations (Sterling IRB, Atlanta, GA, USA), informed consent, and regulations stemming from the Declaration of Helsinki and the International Headache Society (IHS) guidelines for studies of the prevention of migraine.

Subject and Treatment.—Subjects included male and female volunteers with documented histories of CM fulfilling criteria of the Second Edition of the International Classification for Headache Disorders.¹⁴ Subjects were randomized to receive injections of onabotulinumtoxinA plus daily placebo tablets or topiramate and placebo injections. The investigators and study coordinators were blinded to study conditions.

Up to 200 units of onabotulinumtoxinA or placebo were injected with 100 units into fixed loca-

tions and up to an additional 100 units in a “follow the pain” scheme determined at the investigators discretion. Topiramate dosing was initiated at 25 mg daily and escalated to 100 mg in weekly incremental changes of 25 mg. The dosage could be further escalated after one month at the discretion of the investigator to a maximum dosage of 200 mg per day. The average dosage of onabotulinumtoxinA was 109 units for the first injection cycle and the average daily dosage of topiramate was 136 mg by week 12.

Subjects maintained daily headache diaries over a 4-week baseline period and a 12-week active study period. At 12 weeks subjects were re-evaluated and tapered off oral study medications over a 2-week time period. Subjects not reporting a $\geq 50\%$ reduction of headache frequency at 12 weeks were invited to participate in a 12-week open label extension study with onabotulinumtoxinA.

Paper diaries were used throughout the study to record headache frequency, headache severity, start and stop times of headaches, migraine associated symptoms, acute treatment medications and procedures, frequency of visits to emergency/outpatient facilities for headache care, and adverse events. All subjects completed a Migraine Impact & Disability Assessment (MIDAS), Headache Impact Test (HIT-6), and Migraine Impact Questionnaire (MIQ) at baseline, week 4, and 12. Those continuing in the open label extension period repeated these tests at week 26. Investigators completed a 9-point Physician Global Assessment questionnaire at Visit 4 and for those in the open label extension, the assessment was also made at week 26.

Inclusion Criteria

- Outpatients, male or female, of any race, between 18 and 65 years of age
- Female subjects of child-bearing potential with a negative urine pregnancy test who practiced reliable contraception throughout the study period
- Subjects met criteria for CM as defined by Second Edition of the International Classification for Headache Disorders
- Subjects understood all study requirements

Exclusion Criteria

- Female subjects who were pregnant, breast feeding, or planning to become pregnant during the time frame of the study
- Individuals with headache disorders other than CM
- Subjects with medical disorders that increase the risk with exposure to onabotulinumtoxinA
- Subjects with significant liver or renal impairment including kidney stones
- Subjects on ketogenic diets
- Subjects who had previously used botulinum toxin of any type or topiramate regardless of indication
- Subjects with recent evidence of alcohol/drug abuse or overuse of acute medication

Statistical Analysis.—Statistical analyses were performed using SAS version 9 (SAS Institute Inc., Cary, NC, USA).

Sample size was estimated based on a 35% difference in the proportion of all subjects achieving treatment response by Visit 4 (regardless of treatment group assigned) with positive treatment response being defined as a +2 change in Physician Global Assessment (alpha = 0.05, 80% power).

Physician Global Assessment, Response to Treatment: The Investigator will assess response to treatment using the following 9-point scale:

- +4 Clearance of signs and symptoms (about 100% improvement).
- +3 Marked improvement (about 75% improvement).
- +2 Moderate improvement (about 50% improvement).
- +1 Slight improvement (about 25% improvement).
- 0 Unchanged.
- 1 Slight worsening (about 25% worse).
- 2 Moderate worsening (about 50% worse).
- 3 Marked worsening (about 75% worse).
- 4 Very marked worsening (about 100% worse).

The Physician Global Assessment was calculated for each subject at weeks 4 and 12 (see Table 4).

Demographic data were analyzed using two-sided chi-square test or Fisher exact test. Physician Global Assessment and MIQ were analyzed using the Wilcoxon signed rank test. Changes from baseline in

Table 1.—Baseline Characteristics Between Groups

Mean	Headache Diary		
	Total n = 59	Group 1 Topiramate n = 30	Group 2 OnabotulinumtoxinA n = 29
Headache days/month	21.1	20.5	21.8
Headache-free days/month	8.9	9.5	8.2
Migraine days/month	11.1	10.3	11.9
Days on headache meds	14.5	15.1	13.9
Headache severity	2.8	2.7	2.9

Three-point scale: mild, moderate, severe.

headache diaries or MIQ scores were analyzed using ANCOVA/rank ANCOVA based on baseline variability. Paired *t*-test/Wilcoxon signed rank test was used to assess the within group tests for the MIQ.

The study funder generated the random allocation sequence. A sealed card marked with the subject's study number was delivered via FedEx to the Midwestern study site. A research coordinator, not involved with the study, would open the card, note the treatment assignment, dilute the compound, fill the syringe, and hand the medication to the study coordinator who assisted the investigator with the injections. Both the study coordinator and the physician were blinded to the treatment allocation number until the completion of week 12, the end of the blinded study.

RESULTS

Demographics.—There were 59 subjects enrolled (first patient in on 9-2-04 and last patient out on 8-8-06) and were randomized into 2 groups: (Group 1) 30 received topiramate plus placebo injections and (Group 2) 29 received onabotulinumtoxinA injections plus placebo tablets. The mean age was 39.6 years with a range of 19.6 to 64.0; 91.5% were women (54/59). Racially, 94.9% (56/59) were Caucasian. At baseline every subject reported at least one problem with a body system (58/59, neurological; 39/59, psychiatric). A physical/neurological abnormality was found in 13.6% (8/59). The median number of years that subjects suffered with migraine was 16. There were 16

subjects (27%) who identified themselves as smokers: 9 in the Topiramate Group smoked 9.8 cigarettes per day, 7 in the OnabotulinumtoxinA Group smoked 21.4 cigarettes per day.

The average baseline headache characteristics were similar between the 2 groups with 21.1 days per month with headache, 8.9 headache-free days per month, 11.1 migraine days per month, 14.5 days per month on headache medication, and the severity of headache being rates as 2.8 on a 3-point scale (see Tables 1-3).

Participant Flow Diagram

	Double Blind Study		Open Label OnabotulinumtoxinA		
	Week 4	Week 12	Week 14	Week 26	
Randomly Assigned					
Group 1	30	27	22	9	4
Group 2	29	28	22	11	8

Primary Endpoint.—The Treatment Responder Rate based on the Physician Global Assessment indicated that physicians noted improvement in subjects of both groups over time. There was no statistically significant difference between groups (see Table 4) yet the majority of subjects in both groups exhibited improvement. At week 4, in the Topiramate Group, 20/27 (74.0%) had improved compared with 17/28 (60.7%) in the OnabotulinumtoxinA Group. At week

Table 2.—Baseline Characteristics Between Groups

Mean	Study Questionnaire		
	Total	Group 1 Topiramate	Group 2 OnabotulinumtoxinA
MIDAS total score	n = 57 62.67	n = 29 59.17	n = 28 66.29
HIT-6 score	n = 54 65.09	n = 27 65.63	n = 27 64.56
Effectiveness of current treatment	n = 59 n (%)	n = 30 n (%)	n = 29 n (%)
Prescription meds, dissatisfied	18 (30.5)	5 (16.7)	13 (44.8)*
Non-prescription meds, dissatisfied	33 (54.2)	17 (56.7)	15 (51.7)
Frequency of symptoms, dissatisfied	31 (52.5)	14 (46.6)	17 (58.6)*
Severity of symptoms, dissatisfied	26 (44.0)	11 (36.7)	15 (51.7)*
Current preventive tx	n = 58	n = 29	n = 29
Satisfied	7 (12.0)	5 (17.2)	2 (6.8)
Does not apply	24 (41.4)	9 (31.0)	15 (51.7)
Money spent on migraine meds (previous 3 months)	n = 58	n = 30	n = 28
Prescription	320.43	194.20	455.68
Non-prescription	115.58	137.20	93.21

* $P < .05$ (Wilcoxon).

HIT-6 = Headache Impact Test; MIDAS = Migraine Impact & Disability Assessment; tx, treatment.

12, in the Topiramate Group, 17/24 (70.8%) had improved compared with 19/24 (79.2%) in the OnabotulinumtoxinA Group.

Secondary Endpoints.—Headache Days.—The mean number of days per month with headache dropped at week 4 by 4.4 days (from 20.5 to 16.1) for

the Topiramate Group and by 3.0 days (from 21.8 to 18.8) for the OnabotulinumtoxinA Group. This change was not significant between groups but was significant within groups (see Fig. 1). At week 12, the mean number of days per month with headache dropped by 8.1 days to 12.4 in the Topiramate Group

Table 3.—Interference of Migraine Pain at Baseline Between Groups

Mean	Study Questionnaire		
	Total	Group 1 Topiramate	Group 2 OnabotulinumtoxinA
Presenteeism (days/month worked with migraine)	n = 53 27.6	n = 27 24.9	n = 26 30.3
Interference	n = 54 n (%)	n = 27 Quite a bit + extremely n (%)	n = 27 n (%)
Work	22 (40.7)	11 (40.7)	11 (40.7)
Sleep	20 (37.1)	9 (33.3)	11 (40.7)
Mood	27 (51.8)	14 (51.8)	14 (51.8)
Daily activities	30 (55.5)	12 (44.4)	18 (66.7)
Recreational activities	24 (44.4)	10 (37.0)	14 (51.8)
Enjoyment of life	33 (61.1)	17 (62.9)	16 (59.2)

Table 4.—Physician Global Assessment-Response to Treatment

Change from Baseline			
	Group 1 Topiramate n (%)	Group 2 OnabotulinumtoxinA n (%)	P-value
Week 4	n = 27	n = 28	.3221 (Wilcoxon)
No change	4 (14.8)	9 (32.1)	
Slight improvement	8 (29.6)	10 (35.7)	
Moderate improvement	9 (33.3)	3 (10.7)	
Marked improvement	3 (11.1)	4 (14.3)	
Week 12	n = 24	n = 24	.9914 (Wilcoxon)
No change	5 (20.8)	3 (12.5)	
Slight improvement	1 (4.2)	5 (20.8)	
Moderate improvement	6 (25.0)	4 (16.7)	
Marked improvement	10 (41.7)	10 (41.7)	

and by 8.0 days to 13.8 in the OnabotulinumtoxinA Group. This change was not significant between groups but was significant within groups (see Fig. 1).

OPEN LABEL ONABOTULINUMTOXINA TREATMENT (WEEK 14 TO 26).—At week 12, subjects in both groups who had not reduced the

number of headache days per month by $\geq 50\%$ were considered non-responders and were given the option to participate in an open label onabotulinumtoxinA study. Of the 48 subjects who completed the study at week 12, 12/24 (50.0%) in the Topiramate Group and 9/24 (37.5%) in the OnabotulinumtoxinA Group had

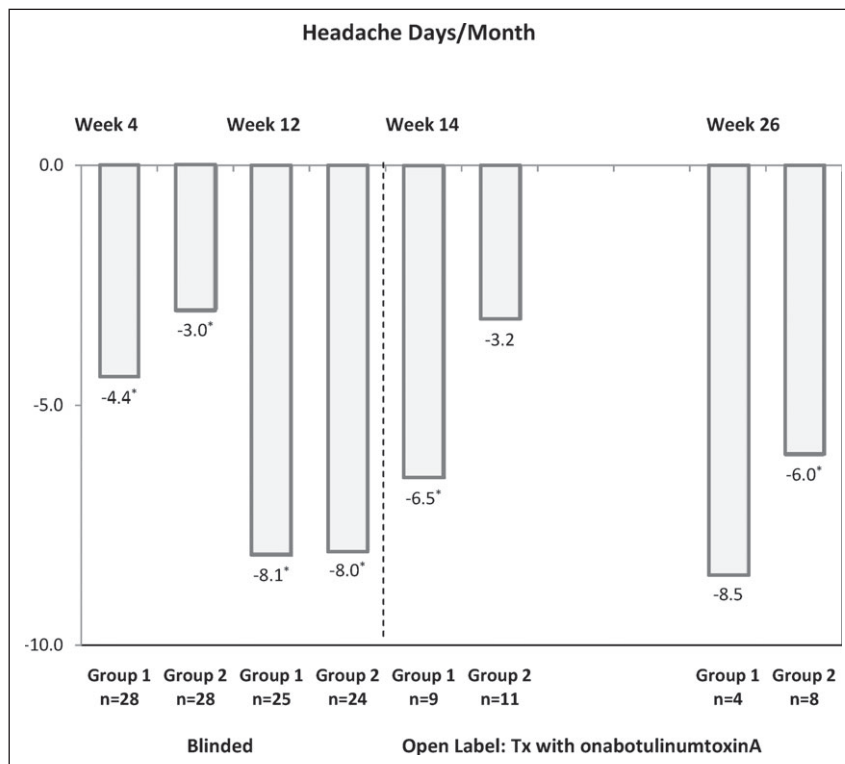


Fig 1.—Change from baseline: headache diary. *P ≤ .05 (t-test within group).

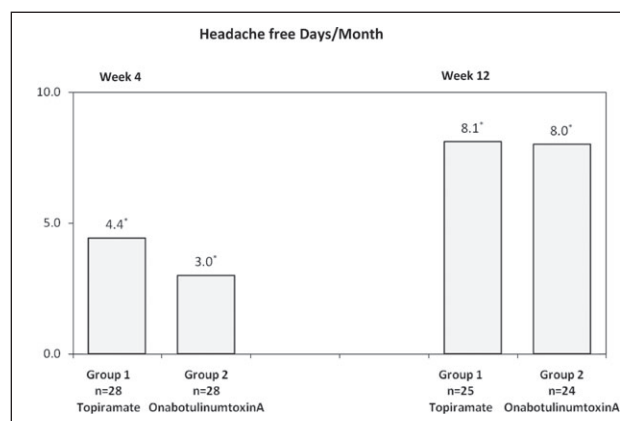


Fig 2.—Change from baseline: headache diary. * $P \leq .05$ (t -test within group).

at least a 50% reduction in headache days per month, according to the headache diaries. Of the remaining 27 subjects, 20 agreed to continue with the open label onabotulinumtoxinA study, 9 from the Topiramate Group and 11 from the OnabotulinumtoxinA Group. By week 26, there were 4 remaining subjects in the Topiramate Group and 8 in the OnabotulinumtoxinA Group. These subjects had a reduction of the number of headache days per month compared to baseline but, according to reports in the diaries, the Topiramate Group had an increase of the average number of headaches days compared with week 14 (1.5 days) while those in the OnabotulinumtoxinA Group had an average reduction (1.04 days) of headache days. This was a significant within-group finding ($P = .0148$).

Headache-Free Days.—The mean number of headache-free days per month increased at week 4 by 4.4 days (from 9.5 to 13.9) for the Topiramate Group and by 3.0 days (from 8.2 to 11.2) for the OnabotulinumtoxinA Group. This change was not significant between groups but was significant within groups (see Fig. 2). At week 12, the mean number of headache-free days per month increased by 8.1 days (to 17.6) in the Topiramate Group and by 8.0 days (to 16.2) in the OnabotulinumtoxinA Group. This change was not significant between groups but was significant within groups (see Fig. 2).

Migraine Disability Assessment.—The average MIDAS total score at week 12 had dropped by 26.67 points for the Topiramate Group and by 38.48 points

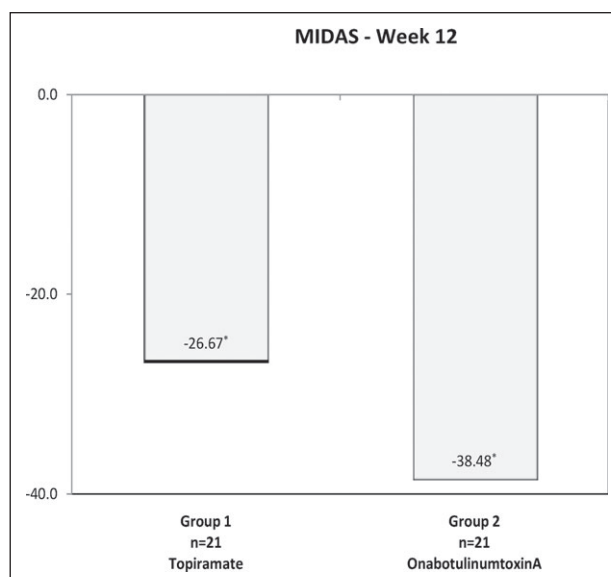


Fig 3.—Change from baseline. * $P \leq .05$ (signed rank within group). MIDAS = Migraine Impact & Disability Assessment.

for the OnabotulinumtoxinA Group. This change was not significant between groups but was significant within groups (see Fig. 3).

Headache Impact Assessment.—The average HIT-6 total score at week 4 had dropped by 5.87 points for the Topiramate Group and by 4.84 points for the OnabotulinumtoxinA Group. This change was not significant between groups but was significant within groups (see Fig. 4). At week 12, the score lessened further by 6.00 points for the Topiramate Group and by 6.29 points for the OnabotulinumtoxinA Group. This change from baseline was not significant between groups but was significant within groups (see Fig. 4).

Money Spent on Migraine Medication.—At week 12, the amount of money spent on prescription drugs over the previous 3 months had decreased by \$121.05 for the topiramate subjects and \$497.60 for onabotulinumtoxinA subjects. This change was not significant between groups but was significant within groups (see Table 5).

Concerning non-prescription drugs, at week 12, subjects estimated the amount of money spent over the previous 3 months had lessened by \$86.86 for the topiramate subjects and \$63.50 for the onabotulinumtoxinA subjects. This change was not significant between groups but was significant within groups (see Table 5).

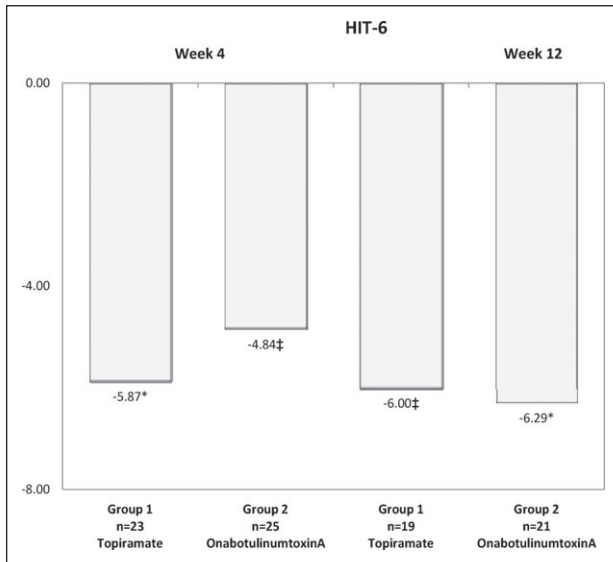


Fig 4.—Change from baseline. * $P \leq .05$ (signed rank within group); ‡ $P \leq .05$ (t -test within group). HIT-6 = Headache Impact Test.

Multiple other endpoints potentially useful to clinician/investigators to evaluate subject response were also collected. These included self-evaluation of presenteeism, interference of migraine at work, and changes in sleep, mood, performance of daily recreational activities, and enjoyment of life. All evaluations listed above demonstrated significant positive change within groups over baseline. While clinician/investigators may have been able to integrate these changes into a cogent understanding of benefit or risk for a specific subject, the statistical basis for these evaluations has not been established and thus the details of the clinical evaluation is not reported on in this manuscript.

Safety Assessments.—The number of subjects who discontinued the study was 15, 8 topiramate subjects and 7 onabotulinumtoxinA subjects, half of whom listed adverse events as the reason for dropping out. Yet at baseline, before the study began, a majority of subjects from both groups had identified side effects (see Table 5).

Table 5.—Safety Assessment Study Questionnaire

n (%)	Group 1 Topiramate	Group 2 OnabotulinumtoxinA
Baseline	n = 30	n = 29
Mild fatigue	22 (73.3)	20 (69.0)
Nausea	22 (73.3)	20 (69.0)
Difficulty concentrating or with memory	19 (63.3)	14 (48.3)
Mood swings	12 (40.0)	14 (48.3)
Week 12	n = 22	n = 22
Mild fatigue	15 (68.2)	16 (72.7)
Nausea	6 (27.3)	13 (59.1)
P -value (χ^2)	.0331*	
Difficulty concentrating or with memory	11 (50.0)	13 (59.1)
Mood swings	6 (27.3)	4 (18.2)

Side Effects of Current Preventive Migraine Treatment: Very Satisfied + Somewhat Satisfied

n (%)	Group 1 Topiramate	Group 2 OnabotulinumtoxinA
Baseline	n = 30	n = 29
	3 (10.0)	4 (13.8)
Week 12	n = 22	n = 22
	9 (40.9)	10 (45.5)
P -value (Wilcoxon)	.2171	

* $P \leq .05$.

At week 12, the 4 most commonly reported adverse events (see Table 5) were mild fatigue, nausea, difficulty concentrating or with memory, and mood swings. The only significant difference between groups was nausea, reported by 27.3% of topiramate subjects and 59.1% of onabotulinumtoxinA subjects (see Table 5).

When asked to rate the influence of current preventive treatment side effects, at baseline, 36.7% of topiramate subjects and 55.2% of onabotulinumtoxinA subjects stated that the question did not apply. At week 12, there was a non-significant change toward being more satisfied with the side effects experienced with the current treatment from 10% to 40.9% among topiramate subjects and from 13.8% to 45.5% among onabotulinumtoxinA subjects.

DISCUSSION

This multi-center pilot study is positive for its primary endpoint of Physician Global Assessment of efficacy and demonstrated similar clinical benefits for both onabotulinumtoxinA and topiramate in subjects with CM. These data support the conclusions of a pilot, single-center study by Mathew and Jaffri.¹⁵

The validity of the Physician Global Assessment in this study was supported by significant correlations with multiple predefined secondary endpoints, including analyses of subjects' diaries and improvement in disability scales. The diary review demonstrated statistically significant decreases in headache days and reduction in acute medication usage from baseline. Further, there was a statistically significant increase in headache-free days. This was true for both topiramate and onabotulinumtoxinA. In addition, both interventions demonstrated statistically significant improvement in MIDAS scores at week 12 (see Fig. 3). Finally there were potentially relevant clinical improvements in quality of life, sleep, work and recreational activities. Given the scope of these changes it appears that the Physician Global Assessment of the subject correlated well with other more traditional statistical measurements of success for preventive therapy defined in this study as secondary endpoints.

Both therapies were generally well tolerated and neither had any associated serious adverse events. Interestingly, adverse events were quite similar for

both medications with only slight differences were noted between the two therapies (see Table 5).

Retention rates for this study were relatively high for the first 12 weeks following the baseline period. Because fewer subjects were eligible to continue in the open label extension, the statistical power of any conclusions for this phase of the study is significantly less. The open label extension should be viewed as an exploratory effort to assess if onabotulinumtoxinA might be beneficial in subjects failing to respond to topiramate. No conclusive statement can be made based on the limited number of subjects in this phase of the study. The most common reasons for study withdrawal were adverse events (53.3%; 8 out of 15) but there were no statistical differences in withdrawal rates between the onabotulinumtoxinA and topiramate groups and only minor differences in specific adverse events between the 2 groups.

Comparisons between the topiramate and onabotulinumtoxinA groups suggested earlier onset of efficacy for topiramate but trended toward greater efficacy for onabotulinumtoxinA at 12 weeks. At week 12, 12/24 (50.0%) of the Topiramate Group and 9/24 (37.5%) of the OnabotulinumtoxinA Group were eligible to continue in the open label extension with onabotulinumtoxinA. Of those originally randomized to topiramate there was statistical improvement at week 14 after open label injection with onabotulinumtoxinA (see Fig. 1). For the group receiving onabotulinumtoxinA as initial therapy, a second injection did not demonstrate increased efficacy at week 14 nor week 26, but there was no worsening of headache frequency. These results must be tempered by the small numbers, the open label design of the extension study, and study design.

The value of a study approximating clinical decision making by utilizing a global physician rating scale is that it permits physicians to integrate and weigh the relative value of various treatment attributes when assessing efficacy. For example, if a specific subject had only a moderate reduction of migraine attacks but acute attacks became more effectively treated with acute intervention resulting in reduction of headache and migraine days and improvement in disability, the investigator could define the subject as a treatment success. Thus, this research methodology more accu-

rately mirrors clinical practice by allowing positive and/or negative outcomes to be appropriately weighted, in the context of the individual subject. This is in contradistinction to more traditional research methodologies where a single primary endpoint is prespecified and success or failure of the patient is determined by that variable alone. Accordingly, if the primary endpoint was for example a 50% reduction in migraine frequency, then a subject with a 40% reduction in migraine frequency but meaningful improvement in disability scores, improved treatment outcome of acute intervention, improvement in quality of life measures, and significant reduction in acute medication need would be deemed a study failure. This paradox opens a debate as to whether the methodology commonly used in regulatory preventive medication studies adequately reflects the real medical needs of patients and clinicians.

At the core of such a debate is the understanding of migraine itself. It is becoming increasingly obvious that within the migraine population there is a spectrum of clinical subtypes that share a common clinical symptomatology but not necessarily share the same underlying pathophysiology or treatment need. For example, the pathophysiology of infrequent acute migraine and CM are likely unique from one another and certainly therapeutic need is distinctly different. In addition, one needs to consider the role of numerous co-morbid diseases and psychosocial consequences that become increasing more prevalent as migraine becomes more chronic. This in turn has the potential to alter efficacy needs for individual patients. Finally, as an understanding of migraine is emerging to suggest that episodic migraine can evolve into a chronic disease (CM) there is a need to assess positive or negative attributes of preventive therapies between as well as during acute episodes of migraine.

Ironically, in 1988 the IHS diagnostic criteria for headache and facial pain syndromes defined migraine only in its episodic form.¹⁶ This is despite defining episodic and chronic definitions for both tension-type and cluster headache. In the 2004 revision of the IHS classification taxonomy, criteria for CM were included and the episodic migraine was considered a precursor to CM.¹⁴ Since then, a more operational

diagnostic scheme has been proposed where for the first time different clinical phenotypes of primary headache are acknowledged as co-existing in defining CM.¹⁷

The primary question is whether migraine-related neurological disruption exists only during attacks of IHS migraine or are there clinical, meaningful, neurological, and physiological alterations evident between attacks of migraine, especially evident as migraine becomes more chronic. This question has critical implications to understanding, effective management, and meaningful scientific study of this disease especially in regard to preventive therapy.

Preventive medications are generally taken on a daily basis and presumably exert pharmacological effects between as well as during migraine attacks. The current regulatory methodology of assessing only attack-related benefit may be unlikely to observe the totality of clinical response. Yet Physician Global Assessment in conjunction with an ability to weigh quality of life evaluations is more likely to detect these potentially positive or negative outcomes associated with preventive treatment. To elaborate this point, in this study numerous non-regulatory migraine endpoints such as improvement in disability scores, decreases in acute medication usage, efficacy of non-prescription medications, and quality of life measures were statistically improved. Clinically these treatment attributes are an important part of the equation for clinicians and patients attempting to evaluate the effectiveness of a specific migraine preventive treatment.

OnabotulinumtoxinA has been studied as a migraine preventive in several clinical trials with sometimes mixed results. This may be because of the novelty of this product in terms of pharmacological mechanisms and delivery. The most recent large scale multi-center study called the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) study was a positive study for subjects with CM.^{12,13} It reduced the number of headache days, acute medication usage, and increased the number of migraine-free days over placebo. Interestingly, studies of subjects with episodic migraine have not been convincingly positive, suggesting disease differences between episodic and CM.

Other studies have demonstrated significant improvement of many quality of life factors with onabotulinumtoxinA vs placebo.¹⁸ These include improvement in MIDAS and HIT-6 scores, sleep, work, and recreational activities. While important, clinically they have doubtful relevance for current standards of regulatory approval.

There are several limitations to this study. One limitation might be that the investigators in the study were more sophisticated in evaluation of migraine response and that Physician Global Assessment by these investigators does not reflect clinical assessment of the broader population of physicians treating migraine. This criticism should however be tempered by the number of objective measures observed in the study, which also support efficacy of onabotulinumtoxinA and topiramate.

A second concern is the use of active comparator rather than placebo and if the positive results reflect regression to the mean. Placebo rates are stated to be 21-23.5% in trials of migraine preventive medications^{19,20} and in general lower response rates are observed in placebo controlled double-blinded studies. Consequently, without an active placebo arm the precise benefit of active treatment arms cannot be fully assessed. On the other hand, topiramate has multiple positive studies and is approved by the FDA for migraine prevention. In the recent PREEMPT studies, onabotulinumtoxinA demonstrated statistical superiority over placebo with a reduction of headache days, which is quite similar to that noted in this study (-8.4 days vs 8.1 days, respectively). Finally, because the intent of this study was to approximate clinical practice the use of a comparator rather than placebo would seem to parallel clinical practice.

Despite these limitations, this study supports onabotulinumtoxinA as an effective preventive treatment for CM with a frequency between 3 and 8 attacks per month. It adds to a body of other studies with similar conclusions.^{21,22} However, there are other clinical studies that do not show efficacy even when similar subjects are enrolled in the study.²³ This suggests that methodological issues as well as pathophysiological considerations of migraine as it becomes increasingly chronified need to be addressed.

CONCLUSIONS

Topiramate and onabotulinumtoxinA demonstrated significant efficacy in treating subjects with CM. Improvements for both medications were noted on a number of clinically relevant measures and reflected in positive Physician Global Assessment of efficacy. The results of this study support onabotulinumtoxinA as a useful therapy for patients with frequent migraine and raise important questions about methodologies and efficacy endpoints used to study migraine preventive medications. Clearly further study of onabotulinumtoxinA and topiramate are warranted.

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