

Research Submissions

Expanding Access to Triptans: Assessment of Clinical Outcome

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Objective.—To evaluate whether access to more liberal quantities of rizatriptan improves clinical outcome in patients with episodic migraine.

Background.—Currently many pharmacy benefit programs limit the number of triptan tablets/injections per month based on perceived cost savings and the belief that too-frequent use of triptans may lead to medication overuse headache and headache chronification.

Methods.—This observer-blind, randomized, parallel-group study enrolled 197 subjects with migraine with or without aura. Subjects completed a 3-month baseline period to establish migraine frequency and then were randomly assigned to receive 9 (formulary limit [FL]) or 27 (clinical limit [CL]) tablets of 10 mg rizatriptan orally disintegrating tablet (ODT) per month for 3 months. The primary endpoint was change in the mean number of migraine days from the baseline to treatment period.

Results.—There was no statistically significant difference between the FL and CL groups in mean number of migraine days (FL-CL LS mean: -0.08 [$-0.39, 0.23$]; $P = .613$). Subjects in the CL group treated attacks at lower headache severity. No CL subjects were reported to have developed chronic migraine despite utilization of greater than 10 rizatriptan ODT tablets per month. Rizatriptan was generally well tolerated by both groups.

Conclusion.—Providing a greater quantity of rizatriptan ODT 10 mg did not reduce the number of migraine days compared with providing 9 tablets per month for this population with episodic migraine with a frequency of 3-8 migraines per month. Regardless of quantity provided, rizatriptan was generally well tolerated.

Key words: rizatriptan, migraine, prescribing limits, triptan tolerability, anticipatory behaviors

Abbreviations: AE adverse event, ANCOVA analysis of covariance, BL baseline, CI confidence interval, CL clinical limit, DISC Disability in Strategies of Care, FAS Full Analysis Set, FL formulary limit, ICHD International Classification of Headache Disorders, NSAID non-steroidal anti-inflammatory drug, TX treatment

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INTRODUCTION

An ongoing clinically important debate concerns the appropriate quantities of acute medication that should be provided to a patient with migraine, particularly for the triptan class of medications. On one side of the debate are those who argue that triptans are costly medications that need to be controlled to prevent unnecessary increases in healthcare costs. This perspective is fueled by research beginning in the mid-1990s that demonstrated a cost savings by limiting triptan quantities for Pharmacy Benefit Programs.^{1,2} Others argue that the cost of triptan medication is justified and offset by the value of the medication and reduction of indirect, non-medication costs associated with migraine.³

In addition, clinicians have cautioned that migraine patients may exhibit anticipatory behaviors, such as treating migraines in anticipation of headache, if provided too liberal access to acute medication, leading to headache chronification and use of abortive medication that may not be clinically appropriate.⁴

Based on these assumptions, pharmacy benefit programs began to restrict the number of triptan tablets/injections per month. Assuming that the average migraineur experiences 4 or fewer migraine attacks per month, many benefit programs concluded that 9 doses (tablets or injections) per month was an appropriate quantity limit for most migraine patients.

Other clinicians argue that quantity limits often promote “hoarding” behaviors in patients that act to prohibit optimal use of these medications.^{5,6} This perspective is important in light of multiple clinical studies that demonstrate increased therapeutic benefits of triptans when administered early during the mild headache phase of a migraine attack.⁷⁻¹⁰ Benefits of early intervention include increased pain-free efficacy, lower recurrence rates, fewer adverse events (AEs), and improved functionality relative to treatment during the moderate to severe headache phase of migraine. Burstein and colleagues demonstrated that triptans administered during an acute migraine attack before the development of cutaneous allodynia resulted in a significant increase in pain-free efficacy.¹¹ Burstein proposed that effective migraine treatment with triptans was a race against time and development of central sensitization.¹²

Further, the Disability in Strategies of Care (DISC) study¹³ demonstrated better efficacy for sumatriptan when administered as the initial treatment for acute migraine and cautioned against step-within-attack care or administering acute therapy in a sequential manner as an attack develops. The US Consortium Guidelines on Acute Migraine Treatment recommend triptans be the first line pharmacologic treatment for moderate to severe migraine or be administered for less severe migraine if over-the-counter treatments were proven ineffective.¹⁴

Despite these recommendations and guidelines, many migraine patients consistently delay administration of acute therapy. In a survey of patients with a pharmacy benefit plan that included triptans, 51% of surveyed subjects stated that they delayed treatment of acute migraine.¹⁵ The most common reasons for delay were “waiting to see if the headache was going to be a migraine” and wanting to treat only if the migraine was “severe.” Interestingly, cost of medication and advice from physicians to treat later in an attack were infrequently mentioned as a reason to delay. A cross-sectional observational study by Golden et al¹⁶ similarly found that the most common reason for not treating early was the desire to reserve medication for a severe migraine (51%), followed by not having medication on hand (35%), health plan quantity limit on drugs (27%), presence of nausea (19%), no access to fluids (17%), and not having privacy (13%).

In clinical practice, patients often concoct complex acute treatment strategies to determine which migraines are worthy of treatment with prescription medications and which pharmacologic interventions are needed to treat specific migraine attacks. These practices often persist after the patient has received advice from the health care professional to treat migraine attacks early with a triptan medication. A commonly heard explanation for this behavior is that the quantity limits imposed by pharmacy benefit plans encourages them to “save” their triptan medications for attacks that most warrant a triptan.

In the present study, we tested the hypothesis that triptan limits impede optimal outcome of acute migraine treatment. It was hypothesized that patients provided with a more liberal quantity of a triptan

medication would treat migraine attacks earlier and consequently experience improved therapeutic outcomes.

METHODS

Study Design.—This was an observer-blind, randomized, parallel-group study of 6 months' duration that enrolled subjects between November 2007 and January 2008. A total of 197 subjects were screened at 4 headache specialty sites and 6 primary care practices. The study was performed in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice. The Sterling Institutional Review Board (Atlanta, GA) reviewed and approved the protocol and 9 investigative sites, and the Thomas Jefferson University Institutional Review Board (Philadelphia, PA) approved the protocol at one site. Written informed consent was obtained from each subject prior to enrollment.

Baseline Period.—During the 3-month unblinded baseline period, all subjects were allotted 9 tablets of rizatriptan orally disintegrating tablet (ODT) 10 mg for acute treatment per month. They were encouraged, though not required, to treat all migraine attacks with rizatriptan and were allowed to rescue after 2 hours with an additional dose of rizatriptan or a non-triptan non-ergotamine product as advised by the investigator. Subjects recorded all migraine attacks, treatment taken, treatment response, and responses to a daily question about presence of migraine and the portion of the day that a headache was present in three 1-month diaries. Diaries were collected and reviewed on a monthly basis, and any unused drug and the container were collected at that time.

Randomized Treatment Period.—At the end of the baseline period, subjects who continued to report an average of 3-8 migraine attacks per month and fewer than 10 headache days per month were randomly assigned (1:1) to receive 1 of 2 different quantities of rizatriptan for acute treatment based on a computer-generated allocation schedule provided by Merck & Co., Inc. To ensure balanced treatment groups, patients were stratified into 2 groups according to the average number of days with migraine per month established during the baseline period: <6

days/month or ≥ 6 days/month. This randomization schedule was a basis for assigning a dose allocation number. Subjects and investigators were blinded to study treatment assignment at randomization; subjects were unblinded upon opening the treatment kit after leaving the investigator's office. Those designated to receive the formulary limit (FL) continued to receive 9 tablets of rizatriptan 10 mg ODT per month, whereas those designated to receive the clinical limit (CL) received 27 tablets of rizatriptan 10 mg ODT per month. As per the product circular for rizatriptan, subjects could use up to 3 tablets of rizatriptan 10 mg in a 24-hour period with at least 2 hours between any 2 doses of rizatriptan. Subjects could retreat a migraine after 2 hours of taking a dose of rizatriptan and could repeat a third dose within 24 hours if needed. Alternatively, they could rescue after 2 hours with a non-triptan non-ergotamine product if approved by the investigator. Subjects recorded migraine attacks, number of tablets taken, treatment response, and responses to a daily question on presence of migraine and portion of the day that a headache was present in three 1-month diaries. Diaries were collected and reviewed on a monthly basis, and any unused drug and the container were collected at that time.

Participants.—For inclusion, subjects had to be at least 18 years of age and have at least a 1-year history of migraine with or without aura diagnosed according to the International Classification of Headache Disorders, 2nd edition (ICHD-2).¹⁷ Subjects also were required to have been using a triptan medication and have a quantity limit of 6-12 tablets per month for the previous 3 months prior to enrollment. All subjects were required to have a frequency of migraine between 3 and 8 attacks per month. Subjects with headache disorders beyond migraine (International Headache Society [IHS] 1.1 or 1.2), such as episodic tension-type headache (IHS 2.1), or subjects with daily or near-daily use of non-steroidal anti-inflammatory drugs, including COX-2 inhibitors, or other analgesics were excluded. Aspirin ≤ 325 mg daily was allowed for cardioprotection.

Hypothesis.—For the treatment of migraine, rizatriptan ODT 10 mg administered based on a CL (27 ODT per month) would be superior to rizatriptan

ODT 10 mg based on a FL (9 ODT per month), as measured by the change from baseline in average number of days with migraine per month (30 days).

Endpoints.—The primary outcome measure was the mean change from the baseline period to randomized treatment period in the number of migraine days per month. Migraine days were calculated by 2 different methods:

- Method 1: Migraine days (primary approach)
 - If a patient reported on the daily diary that they had a headache that lasted all day, it was counted as 1 migraine day.
 - If the headache did not last all day, then only a portion of the day was used in determination of the total number of migraine days:
 - the migraine day contribution was 1/3 if the patient reported the headache lasted “part of the day” and
 - the migraine day contribution was 2/3 if the patient reported the headache lasted “most of the day.”
 - The average number of migraine days per month was then calculated separately for the baseline period and the randomized treatment period by adding the whole days and fractions of days to determine number of migraine days, dividing the number of migraine days by the total number of days in the respective period, then multiplying by 30 to approximate number of days per month.
 - A change from baseline for each patient was then calculated and used to compare patients randomized to the CL with those randomized to receive the FL.
- Method 2: Days with migraine:
 - To assess the sensitivity to the primary approach, a second method considered patients who reported having a headache “part of the day” or “most of the day” as contributing a full migraine day.

Secondary outcome measures were comparisons of the change from baseline (randomized treatment period – baseline period) in mean number of headache attacks, change from baseline in mean attack

duration, mean attack severity, percent of attacks with symptom elimination at 2 hours, change from baseline in the proportion of attacks with elimination of functional impairment at 2 hours, and responder rate in those patients randomized to the CL group vs those randomized to the FL group. Attack duration was defined as the total amount of time from onset of the attack (preceded by at least a 24-hour headache-free period) until the attack terminated (followed by at least another 24-hour headache-free period) regardless of any headache-free intervals lasting less than 24 hours. Attack severity was based on a scale of 0-3 where 0 = No pain, 1 = Mild pain, 2 = Moderate pain, 3 = Severe pain and was documented immediately before the first dose of study medication and at 2 hours after treatment. Elimination of associated symptoms was calculated based on subjects reporting at least one associated migraine symptom (nausea, vomiting, sensitivity to light, or sensitivity to sound) immediately before the first dose of study medication and reporting the resolution of each specific associated symptom at 2 hours after treatment. Elimination of functional impairment was calculated based on subjects reporting mild, moderate, or severe impairment immediately before the first dose of study medication and reporting normal ability to perform activities at 2 hours after treatment. Responder rate (the proportion of patients with at least a 50% reduction in attacks from baseline period to randomized treatment period) was calculated as follows:

$$\% \text{ reduction} = 100\% - [(\text{mean \# attacks during treatment} / \text{mean \# attacks in baseline}) \times 100].$$

Statistical Analyses.—The Full Analysis Set included subjects who recorded at least 7 days of diary data in both the baseline and treatment periods. All efficacy variables were summarized and compared between the 2 randomized treatment groups (CL vs FL). Efficacy measures were analyzed within the framework of analysis of covariance (ANCOVA). The analysis model included study site and the dichotomous baseline number of migraine days (<6 vs ≥6) as covariates and treatment as main effect. The primary presentation of results consists of the model-based estimates and the 2-sided 95% confidence

interval for the treatment difference (FL—CL) constructed from the means and the standard error from the ANCOVA model. Inferential statistics through logistic regression analysis was used to assess the relationship between treatment regimens and a binary outcome such as the presence/absence of 50% reduction in number of attacks from baseline, controlling for potential confounding factors (ie, average number of migraine days per month in baseline period and study site). In this analysis, the probability of a positive outcome (ie, 50% reduction in number of attacks from baseline) was modeled. Treatment group comparison *P* values based on the logistic regression model were displayed with the corresponding odds ratio and 95% confidence interval. Chi-square tests were used to examine bivariate relationships between categorical variables, and Student's *t*-tests were used to compare mean values of continuous variables. Additionally, for all binary outcome measures, percentages of patients by treatment group and differences between treatment groups were displayed. Compliance with study medication was estimated by

the mean number of study medication doses used per month and per attack.

The primary safety analysis compared the incidence of adverse experiences (overall, drug related, and serious) reported in the 2 treatment groups.

The standard deviation assumed for the primary efficacy endpoint was chosen based on a migraine prevention study.¹⁸ With a standard deviation of 5.5 days, a sample size of 80 evaluable patients per treatment regimen would provide 90% power to detect a 2.8-day difference between treatment regimens with respect to the change from baseline in average number of days with migraine per month.

RESULTS

Of 197 migraineurs enrolled into the baseline period, 155 subjects were randomized into the treatment period and reported at least one migraine attack assessment in both periods, meeting criteria defined by ICH E-9 guidance. Of these, 151 subjects had at least 7 days of diary data and were included in the efficacy and safety analyses (Fig.). Baseline

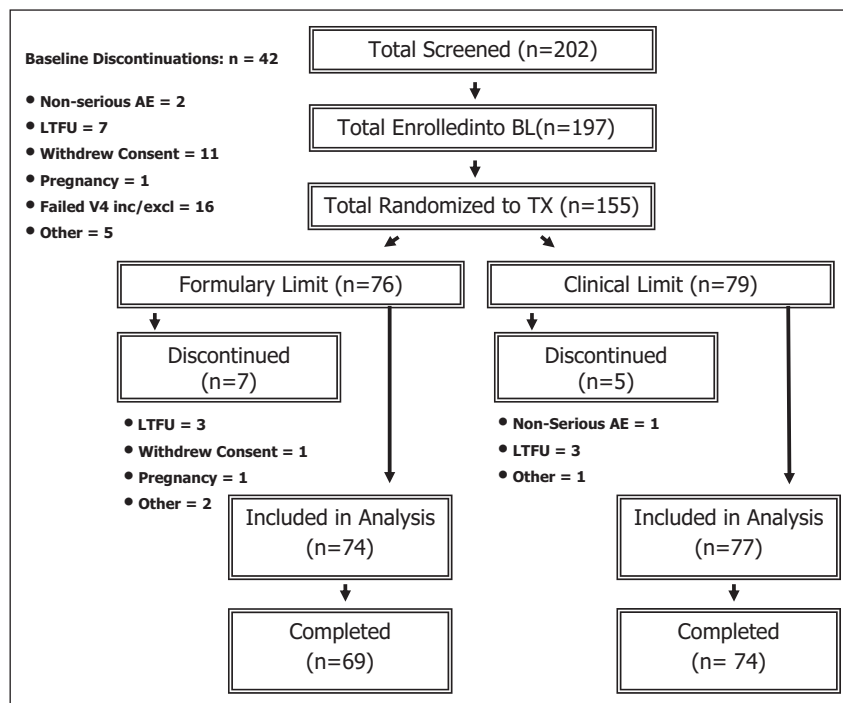


Figure.—Subject accounting. AE = adverse event; BL = baseline; LTFU = lost to follow up; TX = treatment; V4 inc/excl = Visit 4 inclusion/exclusion criteria.

Table 1.—Baseline Demographics

	Formulary limit (9 ODT) n = 74	Clinical limit (27 ODT) n = 77
Sex (n [%])		
Female	65 (87.8%)	66 (85.7%)
Age (years)		
Mean (SD)	40.7 (10.2)	42.2 (11.5)
Range	19-60	18-61
Ethnicity (n [%])		
White	66 (89.2%)	68 (88.3%)
Migraine without aura (n [%])	62 (83.8%)	66 (85.7%)
Migraine with aura (n [%])	18 (24.3%)	18 (23.4%)
#Years since diagnosis		
Mean (SD)	13.1 (10.4)	12.2 (10.1)
Range	0-40	0-37

ODT = orally disintegrating tablet; SD = standard deviation.

characteristics of the study participants in the treatment period are shown in Table 1.

Migraine Days.—The mean number of “migraine days” (method 1) in the FL group decreased from baseline during the randomized treatment period, whereas migraine days in the CL group increased. Neither change was statistically significant (Table 2).

The mean number of “days with migraine” (method 2) in the FL group decreased, whereas the number of days in the CL group increased in the randomized treatment period. This difference between the 2 groups was statistically significant (Table 2).

Migraine Headache Attacks.—The mean number of migraine attacks for subjects decreased from baseline in the FL group and increased from baseline in the CL group during the randomized treatment period. Neither change nor the difference between the FL and CL groups was statistically significant (Table 3).

Attack Duration.—The mean duration of headache associated with migraine attacks for subjects in both the FL and CL groups decreased from baseline during the randomized treatment period. Neither change nor the difference between the groups was statistically significant (Table 3).

Attack Severity.—Mean attack severity score prior to treatment of each attack with study medication in the baseline period was 1.63 for the FL group and 1.61 for the CL group. In the randomized treatment period, the mean attack severity score was 1.63 for FL and 1.56 for CL (not significant). During the treatment period, those in both groups treated a greater

Table 2.—Primary Efficacy Endpoint

	FL (9 ODT) n = 74	CL (27 ODT) n = 77	FL—CL Mean Diff. (95% CI) n = 151	FL-CL LS Mean Difference† (95% CI) P value n = 151
Migraine days per month (method 1)				
BL: Mean (SD)	2.9 (1.2)	2.6 (1.1)		
TX: Mean (SD)	2.7 (1.3)	2.7 (1.3)		
TX—BL: Mean (95% CI)	−0.12 (−0.36, 0.12)	0.06 (−0.16, 0.28)	−0.18 (−0.50, 0.15)	−0.08 (−0.39, 0.23) P value: .613
Days with migraine per month (method 2)				
BL: Mean (SD)	6.2 (1.8)	6.0 (1.9)		
TX: Mean (SD)	5.9 (2.1)	6.4 (2.7)		
TX—BL: Mean (95% CI)	−0.37 (−0.75, 0.004)	0.39 (−0.06, 0.84)	−0.76 (−1.35, −0.18)	−0.63 (−1.22, −0.05) P value: .034

†ANCOVA model assessing treatment regimen, adjusting for stratification based on average number of migraine days per month in BL period (<6 vs ≥6), and study site.

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; CL = clinical limit; FL = formulary limit; LS Mean = least squares mean; SD = standard deviation; TX = treatment.

Table 3.—Number of Headache Attacks and Attack Duration

	FL (9 ODT) n = 74	CL (27 ODT) n = 77	FL-CL Mean difference (95% CI) n = 151	FL-CL LS Mean difference† (95% CI) P value n = 151
Headache attacks/month (24 hours pain free between attacks)				
BL: Mean (SD)	4.6 (1.3)	4.7 (1.4)		
TX: Mean (SD)	4.4 (1.5)	4.9 (2.1)		
TX—BL: Mean (95% CI)	-0.2 (-0.5, 0.01)	0.2 (-0.2, 0.5)	-0.42 (-0.84, 0.003)	-0.41 (-0.83, 0.01) P = .059
Attack duration (hours)				
BL: Mean (SD)	13.3 (7.2)	11.8 (9.1)		
TX: Mean (SD)	12.9 (9.2)	11.6 (8.2)		
TX—BL: Mean (95% CI)	-0.4 (-2.0, 1.2)	-0.2 (-1.8, 1.3)	-0.11 (-2.3, 2.1)	0.35 (-1.7, 2.4) P = .743

†ANCOVA model assessing treatment regimen, adjusting for stratification based on average number of migraine days per month in BL period (<6 vs ≥6), and study site.

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; CL = clinical limit; FL = formulary limit; LS Mean = least squares mean; SD = standard deviation; TX = treatment.

number of attacks during mild headache (CL: 44 of 77 subjects [57.1%]; FL: 33 of 74 subjects [44.6%]). Of 1133 attacks treated in the treatment period by the CL group, 48.6% were treated at mild vs 41.6% in baseline, a 7% increase. Of 985 attacks treated in the treatment period by the FL group, 38.2% were treated at mild vs 38.7% in baseline, a 0.5% decrease. There was a statistically significant difference in favor

of the CL group with greater quantity limits for treating migraine during the mild headache ($P < .0001$) (Table 4).

Elimination of Associated Symptoms and Functional Impairment at 2 Hours.—The level of severe impairment of function was greater in the FL group than in the CL group at baseline; otherwise, the treatment groups had similar baseline values for

Table 4.—Proportion of Headache Attacks Treated at Mild, Moderate, and Severe Pain Levels

		Mild (%)	Moderate (%)	Severe (%)	No headache (%)	Missing (%)	FL-CL†	
							Chi-square	P value
Baseline period	FL (9 ODT) (n = 1064 attacks)	38.7	46.1	10.9	0.19	4.1	6.61	.1583
	CL (27 ODT) (n = 1125 attacks)	41.6	44.7	8.8	0.0	4.9		
Treatment period	FL (9 ODT) (n = 985 attacks)	38.2	45.8	11.3	0.10	4.7	64.27	<.0001
	CL (27 ODT) (n = 1133 attacks)	48.6	41.7	9.4	0.18	0.18		

†Significance of differences was assessed via chi-square test.

BL = baseline; CL = clinical limit; FL = formulary limit; TX = treatment.

Table 5.—Elimination of Associated Symptoms and Functional Disability at 2 Hours

		FL (9 ODT) n = 74	CL (27 ODT) n = 77	FL-CL†	
				Chi-square	P value
Associated symptom					
Nausea	BL	270/371 (73%)	331/451 (73%)	0.039	.84
	TX	293/390 (75%)	291/437 (67%)	7.2	.007
	Change	2.35%	-6.8%		
Vomiting	BL	30/37 (81%)	39/45 (87%)	0.47	.490
	TX	29/42 (69%)	24/33 (73%)	0.12	.728
	Change	-12.03%	-13.94%		
Photophobia	BL	512/789 (65%)	480/764 (63%)	0.72	.397
	TX	459/757 (61%)	478/811 (59%)	0.47	.494
	Change	-4.26%	-3.89%		
Phonophobia	BL	384/591 (65%)	451/648 (70%)	3.00	.083
	TX	344/571 (60%)	424/661 (64%)	1.98	.159
	Change	-4.72%	-5.45%		
Degree of impairment					
Mild	BL	316/474 (67%)	348/548 (63%)	1.12	.290
	TX	266/379 (70%)	378/569 (66%)	1.47	.225
	Change	3.5%	2.9%		
Moderate	BL	113/317 (36%)	130/339 (38%)	0.51	.474
	TX	121/349 (35%)	124/350 (35%)	0.04	.834
	Change	0.98%	-2.9%		
Severe	BL	20/86 (23%)	6/73 (8%)	6.53	.011
	TX	15/98 (15%)	14/98 (14%)	0.04	.841
	Change	-7.9%	6.1%		

†Significance of differences was assessed via chi-square test.

BL = baseline; CL = clinical limit; FL = formulary limit; TX = treatment.

associated symptoms and functional disability. Among subjects randomized to FL or CL, there was a non-significant decrease in elimination of most of the associated symptoms and elimination of functional impairment in the treatment period regardless of the number of baseline attacks (Table 5).

Responder Rate.—Subjects in the CL group (7.8%) were more likely to have a 50% reduction from baseline in the number of attacks per month than those in the FL group (2.7%), but the difference was not statistically significant (odds ratio: 3.27 [0.63, 17.07], $P = .106$).

The mean number of doses of study medication used per month in the FL group decreased in the treatment period vs baseline period (not significant; Table 6). In contrast, the mean number of doses of study medication used per month in the CL group significantly increased during the treatment period ($P = .0001$; Table 6). Use of other acute migraine

treatment medications decreased from 5.6 doses in the baseline period to 3.5 doses per month in the acute treatment period in the FL group and from 5.7 doses per month during the baseline period to 3.5 doses per month during the treatment period in the CL group. Overall, the quantity of acute migraine medication considering both rizatriptan and other medications did not appear to change throughout the baseline or treatment periods in the CL group.

Only 0.5% of migraine attacks were treated prior to the onset of headache, and there was no difference between the FL and CL groups. This suggests that anticipatory behaviors did not occur through the time span of this study despite access to rizatriptan and encouragement to treat attacks early.

Safety Evaluation.—The AE profile for the baseline and treatment periods was similar for subjects receiving FL vs CL of rizatriptan. No unexpected AEs were reported in either group. Three subjects

Table 6.—Study Medication Doses Used Per Month

	FL (9 ODT) n = 74	CL (27 ODT) n = 77	FL-CL Mean difference (95% CI) n = 151	FL-CL LS Mean Difference†(95% CI) P value n = 151
BL: Mean (SD)	6.7 (1.7)	6.5 (1.8)		
TX: Mean (SD)	6.6 (2.1)	8.6 (4.5)		
TX—BL: Mean (95% CI)	-0.14 (-0.58, 0.30)	2.10 (1.31, 2.89)	-2.24 (-3.15, -1.33)	-2.31 (-3.23, -1.40) Pvalue < .0001

†ANCOVA model assessing treatment regimen, adjusting for stratification based on average number of migraine days per month in BL period (<6 vs ≥6), and study site.

ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; CL = clinical limit; FL = formulary limit; LS Mean = least squares mean; SD = standard deviation; TX = treatment.

discontinued due to AEs (abdominal cramping and somnolence [baseline period]; heart palpitations [treatment period]). Abdominal cramping was not considered related to study drug; heart palpitations and somnolence were considered to be possibly related to study drug. There were no subject withdrawals due to worsening of migraine or development of chronic migraine. Overall, rizatriptan was generally well tolerated, and numerically fewer AEs were reported during the treatment period than in the baseline period. There were 6 reports of serious AEs (cholelithiasis, appendicitis, chest pain, paresthesia, hypoesthesia, and ketoacidosis) by 4 subjects during the baseline period. None were considered related to study drug, and 3 of the 4 subjects were randomized to treatment. No subjects withdrew from the study due to serious AEs.

DISCUSSION

The underlying premise of this study was that if migraineurs had access to greater quantities of a triptan, they would treat acute migraine earlier, when pain was mild, and, as a consequence, experience a measurable improvement in treatment outcome. However, the data suggest few statistically significant differences between the group receiving 9 vs 27 tablets of rizatriptan, and the primary endpoint for this study was not satisfied. Rizatriptan was generally well tolerated regardless of quantity limits, and no

specific AEs were evident in the population utilizing greater than 9 tablets of rizatriptan per month for 3 months.

A few secondary endpoints, however, did reach statistical significance. For example, subjects randomized to the CL group were more likely to take the study medication at a lower pain severity than those in the FL group in the treatment period; however, this difference was not statistically significant in the baseline period. This trend toward intervention at less intense levels of headache was a desired outcome, although it did not appear to statistically diminish the number of migraine days. Also, the mean number of doses of study medication used per month in the CL group significantly increased during the treatment period compared with that for the FL group.

There was a suggestion of benefit for the CL (27 tablets), compared with the FL (9 tablets), for a small subpopulation of subjects who reported >50% reduction in migraine frequency. Given the small number of subjects in this subpopulation, further study will be necessary before any conclusive statement can be made.

Although subjects randomized to the CL of rizatriptan did use greater quantities of rizatriptan in the treatment period of the study, they used fewer other acute migraine treatments, and there was no evidence of any untoward AEs between the CL and FL groups. Nor was there evidence of anticipatory behaviors in

migraine treatment, as almost all subjects did not treat in anticipation of headache and returned unused quantities of drug.

Several limitations of this study are noteworthy and may help explain the results observed. First, the study design may have had a selection bias toward a study population of migraine subjects that, based on their migraine frequency, did not require an increase in abortive treatment. This is supported by the observation that, in the CL group, only 53% of subjects utilized all 9 doses of rizatriptan in the baseline phase and only 2 (2.6%) used all 27 doses of rizatriptan in the treatment phase, thus suggesting that the supply of rizatriptan significantly exceeded treatment need in this population of migraine sufferers. This result suggests that the actual population potentially requiring a greater number of rizatriptan tablets was significantly smaller than anticipated in the statistical analysis plan and, thus, the study was probably underpowered to assess its primary endpoint.

The rationale for selecting subjects with fewer than 8 migraines per month and 10 treatment days of acute medication was twofold and underscores the clinical dilemma of quantity standards in clinical practice. The first intent was to ensure that subjects had episodic rather than chronic migraine, and the second was to have subjects enrolled in the study utilizing quantities of acute medications below the quantity threshold for triptan usage established by the IHS criteria in the definition of medication overuse headache.¹⁷ Given these limitations, the population included in the study was, on average, experiencing between 4 and 5 migraines per month. It is highly likely that many subjects with this frequency of migraine would have acute treatment needs met by the FL of 9 tablets per month.

Efforts were made, through post hoc analyses, to evaluate subpopulations with more frequent migraine attacks, but the population size was too small to make any meaningful statistical conclusions (data not shown). In addition, the population recruited into this study was not queried about whether they engaged in any hoarding behaviors with their triptans prior to study entry. Thus, a flaw in this study may have been that it failed to study a population where greater than 9 tablets of

rizatriptan per month was clinically necessary and might have made a difference in outcome.

Another important limitation was the absence of a quality-of-life measure in the study design. It may well be that measurable benefit that is relevant to patients and clinicians would be observed outside the standard efficacy measures of clinical studies. Other studies in migraine have demonstrated benefit to migraine patients beyond simply frequency of attacks or 2-hour pain-free efficacy in response to acute treatment, and it may be that broader evaluations of treatment efficacy need to be utilized in future studies.^{19,20}

Additional clinical nuisances observed in the study data are worthy of discussion. Considerable debate is evident among headache specialists about the appropriate quantities of acute medication that should be used by migraine patients.²¹ In a 2000 guideline for primary care providers, a limit of triptan use was suggested at 2 or fewer days per week.²² This limit was also suggested by Silberstein.²³ In the revised ICHD-2 diagnostic criteria for medication overuse headache secondary to triptan overuse, a quantity of 10 treatment days per month was defined as the threshold for overuse.²⁴ These guidelines, though consensus-based and derived from different perspectives, are nonetheless highly consistent. Challenging the assumption that utilization of quantities of greater than 10 days of a triptan per month is always associated with a poor clinical outcome, Shettell et al suggested that improved quality of life is noted with daily naratriptan use in a carefully selected population of chronic migraine patients.²⁵ This debate is further fuelled by epidemiologic data from Scher and Lipton on migraine chronification that demonstrated that the frequency of migraine attacks can wax and wane as part of the natural history of migraine even when medication is controlled.^{26,27}

Despite published guidelines and the clinical debates over the role of acute medication in the etiology of medication overuse headache, medication overuse continues to be a significant problem, with an estimated 80% or more of patients seen in tertiary headache clinics being diagnosed with medication overuse headache.²⁸ In addition, many headache specialists have advised caution about anticipatory

behaviors in the migraine population leading to taking abortive medication that may not be needed and suggested the need for clinicians, not patients, to determine the quantity they need for acute treatment of migraine.²⁹

CONCLUSION

This study failed to demonstrate clinical reduction of migraine days or migraine attacks in this population of subjects with episodic migraine with a frequency of 3-8 migraines per month when supplied with 27 vs 9 tablets of rizatriptan ODT per month. However, subjects receiving 27 tablets of rizatriptan did treat during the mild headache phase of the migraine attack more often than those receiving 9 tablets per month and appeared to prefer triptans over non-triptans for treatment of migraine. Subjects with 27 tablets used more rizatriptan, but this appeared to be well tolerated. There were no safety concerns or an increase in AEs. Whether there is a subpopulation of migraineurs whose clinical outcome would be altered in a positive fashion if greater quantities of triptan were provided needs to be determined in future studies.

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