

Research Submission

Characteristics of Migraine Attacks and Responses to Almotriptan Treatment: A Comparison of Menstrually Related and Nonmenstrually Related Migraines

Merle L. Diamond, MD; Roger K. Cady, MD; Lian Mao, PhD; David M. Biondi, DO; Gary Finlayson, RPh; Steven J. Greenberg, MD; Pamela Wright, RN

Objectives.—To compare the clinical characteristics of menstrually related migraines (MRMs) and nonmenstrually related migraines (nonMRMs) and to investigate the efficacy of almotriptan in the treatment of these migraine subtypes.

Design/Methods.—These are *post hoc* analyses of data from the AXERT[®] Early miGraine Intervention Study (AEGIS), a multicenter, double-blind, parallel-group trial that evaluated adults with IHS-defined migraine with and without aura. Patients were randomized 1:1 to treat 3 consecutive headaches with almotriptan 12.5 mg or matching placebo at the first sign of headache typical of their usual migraine, at any level of pain intensity but within 1 hour of onset. MRMs were defined as those occurring ± 2 days of the first day of menstrual flow. *Post hoc* analyses to describe headache characteristics pooled all migraine attacks experienced by patients who reported ≥ 1 menses during the study regardless of assigned treatment group. The *post hoc* efficacy analyses included outcomes of almotriptan treatment compared with placebo treatment for all migraines in patients with a menstrual record.

Results.—Of the 275 women in the AEGIS intent-to-treat population, 190 (69.1%; 97 almotriptan, 93 placebo; aged 18-54 years) reported ≥ 1 menses during the trial. Of the 506 migraines reported by these patients, 95 (18.8%) occurred ± 2 days of the first day of menstrual flow and were defined as MRM. Aura was associated with 11.7% of MRM and 15.0% of nonMRM. Allodynia-associated symptoms were present with 62.8% of MRM and 57.0% of nonMRM. Prior to treatment, 19.1% of MRM were associated with normal functional ability, 68.1% with disturbed functional ability, and 12.8% required bed rest compared with 18.9%, 68.8%, and 12.3%, respectively, of nonMRM. Pretreatment pain intensity was mild in 40.0%, moderate in 47.4%, and severe in 12.6% of MRM compared with 43.6%, 47.2%, and 9.2%, respectively, of nonMRM. Almotriptan treatment efficacy outcomes for MRM vs nonMRM, respectively, were: 2-hour pain relief, 77.4% vs 68.3%; 2-hour pain free, 35.4% vs 35.9%; and sustained pain free, 22.9% vs 23.8%. Almotriptan was similarly effective in relieving migraine-associated symptoms and improving functional disability associated with both MRM and nonMRM.

Conclusions.—Prior to treatment, the presence of migraine-associated characteristics including aura, allodynia-associated symptoms, photophobia, phonophobia, and nausea were similar for both MRM and nonMRM attacks. The pretreatment levels of pain intensity and functional disability were likewise similar across the migraine subtypes. Almotriptan was equally effective in the treatment of both MRM and nonMRM attacks and was associated with an adverse event profile that was similar to placebo treatment.

Key words: menstrual migraine, almotriptan, treatment

Abbreviations: AAS allodynia-associated symptoms, AE adverse event, AEGIS AXERT[®] Early miGraine Intervention Study, MRM menstrually related migraine, nonMRM nonmenstrually related migraine, SPF sustained pain free

(*Headache* 2008;48:248-258)

From the Diamond Headache Clinic, Chicago, IL, USA (M. Diamond); Headache Care Center, Springfield, MO, USA (R. Cady); Ortho-McNeil Janssen Scientific Affairs, Titusville, NJ, USA (L. Mao, D. Biondi, G. Finlayson, S. Greenberg, and P. Wright).

Address all correspondence to M. Diamond, The Diamond Headache Clinic, LTD., 467 West Deming Place, Chicago, IL 60614, USA.

Accepted for publication October 19, 2007.

For conflict of interest, see next page.

Conflict of Interest: Merle L Diamond, MD, is a consultant for GSK, Merck, Ortho-McNeil, and Primary Care Network; advisory board member for AstraZeneca, GSK, Ortho-McNeil, and Primary Care Network; speakers bureau member for AstraZeneca, GSK, Merck, Ortho-McNeil, Pfizer, and Primary Care Network; received research grants from AstraZeneca, GSK, Merck, Ortho-McNeil. Roger K. Cady, MD, is a consultant for Aradigm Corp, GSK, Jazz Pharmaceutical and Ortho-McNeil; advisory board member for Allergan, Atrix Labs, Capnia, Endo, GSK, Johnson & Johnson, Medpointe, Merck, Ortho-McNeil, and Winston Labs; received research grants from Abbott, AdvanceBionics, Alizyme, Allergan, Alexza, Aradigm Corp, Capnia, Cipher, Eisai, Endo, GelStat, GSK, Jazz Pharmaceutical, Johnson & Johnson, MAP Pharmaceutical, Matrixx, Merck, Neuralie, Novartis, Ortho-McNeil, Pfizer, Pozen, Schwartz, Torrey Pines, and Vernalis.

Lian Mao, PhD; David M Biondi, DO; Gary Finlayson, RPh; Steven J Greenberg, MD; Pamela Wright, RN are employees of Ortho-McNeil Janssen Scientific Affairs, LLC, Titusville, New Jersey.

INTRODUCTION

Migraine is a chronic neurological disorder with a prevalence of 18.2% in females and 6.5% in males in the United States.¹ The American Migraine Study II reported that, in the ages studied (≥ 12 years), migraine prevalence was greater in females than in males across the life span and increased from age 12 to 40, after which it began to decline.¹ A temporal relationship between the normal physiologic reproductive cycle and the prevalence of migraine over a woman's life span has suggested that there is an association between female sex hormones and migraine. However, while epidemiologic, pathophysiologic, and clinical evidence links estrogen to migraine headaches, the evidence for the effectiveness of estrogen supplementation or manipulation as a preventive treatment for menstrual migraine has been inconsistent,² and consequently hormone treatment is not recommended as a first-line treatment strategy for most women with migraine.³

Many women with migraine report an increase in the frequency of headaches around the time of their menses.^{4,5} However, prior to publication of diagnostic criteria for menstrual migraine in the second edition of the International Classification of Headache Disorders (ICHD-2) in 2004,⁶ this disorder was inconsistently defined thereby making it difficult to compare the results of various clinical reports and trials. The ICHD-2 defines pure menstrual migraine as headaches meeting the diagnostic criteria for migraine without aura, and occurring ± 2 days of the first day of menstrual flow in at least 2 out of 3 menstrual cycles and at no other times during the cycle. Menstrually related migraines (MRMs) are defined as above but occur in women who also experience migraines at other times during their menstrual cycle. A recent

systematic review reported that among female migraineurs, the prevalence of pure menstrual migraine was 3.5-12% and that of MRM was approximately 50%.²

While some studies report that MRMs are more severe, of longer duration, and associated with more functional disability compared with migraines at other times during the menstrual cycle,^{7,8} a study by Stewart et al does not support these findings.⁹ Furthermore, although MRMs have been reported to be more resistant to treatment than nonmenstrually related migraine (nonMRMs),^{7,8} several retrospective and prospective clinical trials have reported successful acute treatment of MRMs with sumatriptan, zolmitriptan, rizatriptan, and almotriptan with no significant differences in treatment outcome being observed.¹⁰⁻¹⁶

It is difficult to evaluate the scientific literature to determine if MRMs are more severe and resistant to treatment than nonMRMs because of the differences in headache definitions and trial methodology used to assess these factors. The definitions of menstrual migraine (ie, the range of days included before and/or after the onset of menstrual flow) vary among these trials, some are prospective while others are retrospective, some recruited patients from the general population while others examined patients referred to specialty headache clinics, and some studies included patients with tension-type headache and chronic daily headache in addition to migraine. In addition, studies have not assessed outcome beyond 24 hours.

In this analysis, we sought to characterize MRMs using data from the AXERT[®] Early miGraine Intervention Study (AEGIS). The results from AEGIS have previously been reported, demonstrating that acute treatment with almotriptan within 1 hour of migraine onset results in significantly better efficacy

outcomes compared with placebo with a tolerability profile similar to placebo.¹⁷ This current report includes *post hoc* analyses of data from all migraine attacks experienced by female patients who had ≥ 1 menses during the AEGIS trial. The objective of this *post hoc* analysis is twofold: to compare the clinical characteristics of MRM and nonMRM and to investigate the efficacy of almotriptan in the treatment of these 2 migraine subtypes.

METHODS

Study Design.—The AEGIS trial was a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial conducted in 37 centers in the United States.¹⁷ Eligible patients were randomized in a 1:1 ratio to treat 3 consecutive migraine attacks with either almotriptan 12.5 mg or matching placebo. Patients were instructed to self-administer their assigned study medication at the first sign of headache pain typical of their usual migraine, at any level of pain intensity but within 1 hour of onset. Patients used a personal digital assistant to record responses to a standardized battery of questions related to pain intensity, photophobia, phonophobia, nausea, vomiting, allodynia-associated symptoms (AAS), and level of functional disability at multiple time points during their headaches both before and after treatment with study medication.

The complete lists of inclusion and exclusion criteria have been described previously.¹⁷ Key inclusion criteria were: patients 18-65 years of age, a history of IHS-defined migraine of at least moderate pain intensity with or without aura for ≥ 1 year, and an average monthly migraine headache frequency of 2-6 for the 3 months prior to enrollment. Key exclusion criteria were: an average of ≥ 15 headache days/month in the 6 months prior to enrollment, contraindication to almotriptan or other triptan class medications, previous discontinuation of almotriptan therapy due to adverse event (AE) or lack of efficacy, and patients with a history of headache pain medication overuse.

Post hoc analyses were performed using data from all migraine attacks experienced by female patients who had ≥ 1 menses during the trial. In addition, paired analyses were performed using data from female patients who had at least 1 MRM and 1

nonMRM during the trial and the pair occurred in succession with no particular order. MRMs were defined as those which occurred ± 2 days of the first day of menstrual flow.

Definition of Endpoints and Other Measurements.—Patients reported the presence or absence of migraine-associated aura and the migraine-associated symptoms of phonophobia, photophobia, and nausea. Patients also reported the presence of pretreatment AAS, defined as head or face pain or scalp tenderness in response to touch or pressure that usually does not cause pain, such as wearing eyeglasses, combing their hair, wearing a hat, or lying down on the side where headache is located. Patients rated their level of pretreatment and posttreatment functional ability using the following categories: can perform normal activities; normal activities disturbed but can continue to work; normal activities disturbed and bed rest required; or emergency room visit or hospitalization required.

The primary efficacy endpoint was pain free at 2 hours posttreatment for the first headache, defined as a decrease in baseline pain intensity from severe, moderate, or mild, to no pain, without the use of supplemental pain medication and/or anti-emetic medication. The secondary efficacy endpoints for this analysis are pain relief at 2 hours posttreatment, defined as a decrease in baseline pain intensity from severe or moderate to mild or no pain, without the use of supplemental pain medication and/or anti-emetic medication, and sustained pain free (SPF), defined as pain free at 2 hours posttreatment with no recurrence of moderate or severe headache pain over the ensuing 2-24 hours, with no use of supplemental pain medication and/or no use of anti-emetic medication through 24 hours posttreatment.

Statistical Analyses.—All inferential statistical tests were 2-tailed and employed a tolerance for Type I error of 0.05. No adjustments were made for multiplicity. Efficacy summaries and analyses used the evaluable for efficacy population of patients, defined as all randomized patients who took study medication and had evaluable baseline and 2-hour posttreatment headache pain intensity data. The *post hoc* analyses to describe headache characteristics included all migraine attacks for patients who

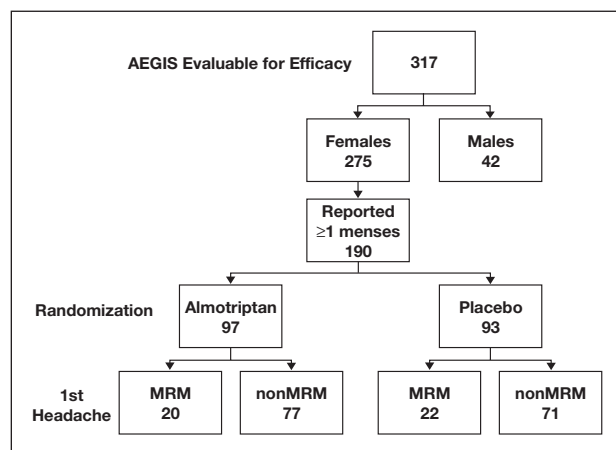


Fig 1.—Patient disposition. AEGIS, AXERTI® Early miGraine Intervention Study; MRM, menstrually related migraine; nonMRM, nonmenstrually related migraine.

reported ≥ 1 menses during the study regardless of assignment to almotriptan or placebo treatment. The *post hoc* efficacy analyses also included outcomes of almotriptan treatment compared with placebo treatment for all migraines in patients with a menstrual record. Inferential statistical tests were performed for each migraine attack, while descriptive analyses were used to summarize outcomes from multiple migraine attacks. For each attack, the pretreatment reports of aura, AAS, migraine-associated symptoms, functional level, and pain intensity; and the posttreatment percentage of headaches achieving 2-hour pain free, 2-hour pain relief, SPF, and return to normal function, were compared between groups (MRM vs nonMRM) using a Cochran-Mantel-Haenszel general association test adjusting for pooled center.

RESULTS

Patients.—Of the 317 patients comprising the evaluable for efficacy population in the AEGIS trial, 275 (86.8%) were female (Fig. 1). Of these 275 females, 190 (69.1%) reported ≥ 1 menses during the trial, 97 from the almotriptan-treatment group and 93 from the placebo-treatment group. This population of 190 patients reported a total of 506 migraines during the trial: 95 migraines (18.8%) occurred ± 2 days of the first day of menstrual flow and were defined as MRM, while 411 migraines (81.2%) occurred > 2 days before or after the first day

of menstrual flow and were defined as nonMRM. When evaluating the origins of the headache totals for each subtype, 75 women (39.5%) recorded 1 MRM, 10 women (5.3%) recorded 2 MRMs, no woman (0%) recorded 3 MRMs, and 105 women (55.3%) recorded nonMRM only.

To evaluate population demographics of the 190 women included in these analyses, patient descriptive data were derived from the first study headache and it was stratified by migraine subtype. Of the 97 women who received almotriptan treatment, 20 reported MRM and 77 reported nonMRM; of the 93 women who received placebo treatment, 22 reported MRM and 71 reported nonMRM. The demographic parameters of age, race, height, and weight were similar for the 42 patients who reported MRM compared with the 148 who reported nonMRM for their first migraine attack (Table 1). Similar demographic parameters stratified by migraine subtype were found in analyses of the almotriptan-treatment group population that included 20 women who reported MRM and 77 women who reported nonMRM for their first migraine attack.

Migraine Headache Characteristics.—The pretreatment characteristics of MRM were similar to those of nonMRM. In a pooled analysis of all migraine attacks, pretreatment aura was associated with 11.7% of MRM and 15.0% of nonMRM (Fig. 2). In the pooled analysis, pretreatment AAS were reported with 62.8% of MRM compared with 57.0% of nonMRM (Fig. 2). In the independent analyses of each of the 3 migraine attack groups, no statistically significant differences were seen between MRM and nonMRM with regard to the proportion of attacks associated with aura ($P = .231$ for attack 1, $P = .564$ for attack 2, $P = .901$ for attack 3) or AAS ($P = .190$ for attack 1, $P = .443$ for attack 2, $P = .309$ for attack 3).

In a pooled analysis of all migraine attacks, MRM and nonMRM were similar with regard to the proportion of attacks associated with phonophobia, photophobia, or nausea. For MRM vs nonMRM, pretreatment phonophobia was reported in 71.3% vs 75.4% of attacks, pretreatment photophobia in 84.0% vs 78.9% of attacks, and pretreatment nausea in 40.4% vs 33.4% of attacks, respectively (Fig. 2).

Table 1.—Patient Demographics†

	MRM‡ (n = 42)	nonMRM (n = 148)	Total (N = 190)
Age (year), mean (range)	35.6 ± 8.54 (21-52)	35.9 ± 8.53 (18-54)	35.9 ± 8.51 (18-54)
Race, n (%)			
White	36 (85.7)	119 (80.4)	155 (81.6)
Black	5 (11.9)	21 (14.2)	26 (13.7)
Hispanic	1 (2.4)	5 (3.4)	6 (3.2)
Asian	0	3 (2.0)	3 (1.6)
Weight (lbs.), mean (range)	162.4 ± 45.07 (106.0-311.0)	165.2 ± 36.77 (102.0-264.0)	164.6 ± 38.66 (102.0-311.0)
Height (inch), mean (range)	64.4 ± 2.57 (60.0-70.0)	64.8 ± 2.69 (58.0-71.0)	64.7 ± 2.66 (58.0-71.0)

†Patients with first migraine attack and with menstrual records.

‡MRM defined as migraine headaches that occurred ±2 days of the first day of menstrual flow.

MRM, menstrually related migraine; nonMRM, nonmenstrually related migraine.

Pretreatment headache pain intensity was mild in 40.0%, moderate in 47.4%, and severe in 12.6% of all MRMs compared with 43.6%, 47.2%, and 9.2%, respectively, of all nonMRMs (Fig. 3), notwithstanding the early treatment paradigm, in which patients were instructed to take the study medication at the first sign of headache pain typical of their usual migraine, within 1 hour of onset. In the independent analyses of each of the 3 migraine attack groups, MRMs were found to be associated with a significantly higher level of pain intensity ($P = .017$) compared with nonMRMs in attack 1; for attacks 2 and 3,

there were no statistically significant differences between the overall level of pain intensity of MRM and nonMRM.

In a pooled analysis of all migraine attacks, prior to treatment 19.1% of MRM were associated with a normal level of function, 68.1% with a disturbed level of function, and 12.8% required bed rest compared with 18.9%, 68.8%, and 12.3%, respectively, of nonMRM (Fig. 4). In the independent analyses of each of the 3 migraine attack groups, MRMs were found to be associated with a significantly higher level of functional disability ($P = .014$) compared with

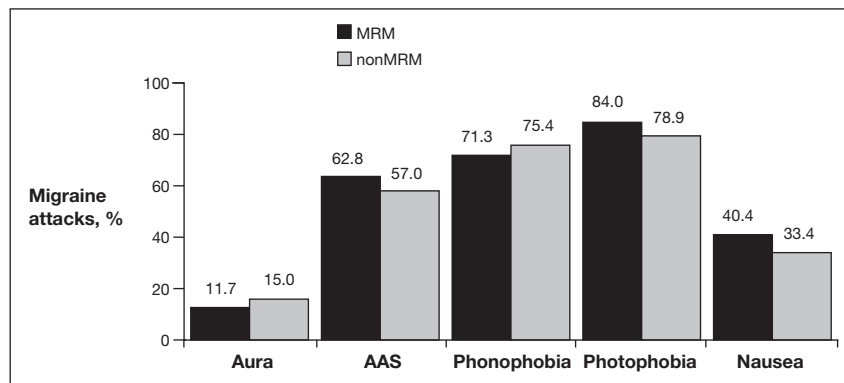


Fig 2.—Pretreatment characteristics of menstrually related migraine (MRM) and nonmenstrually related migraine (nonMRM). Proportion of MRMs and nonMRMs with pretreatment aura, allodynia associated symptoms (AAS), phonophobia, photophobia, and nausea: all attacks and treatment groups combined.

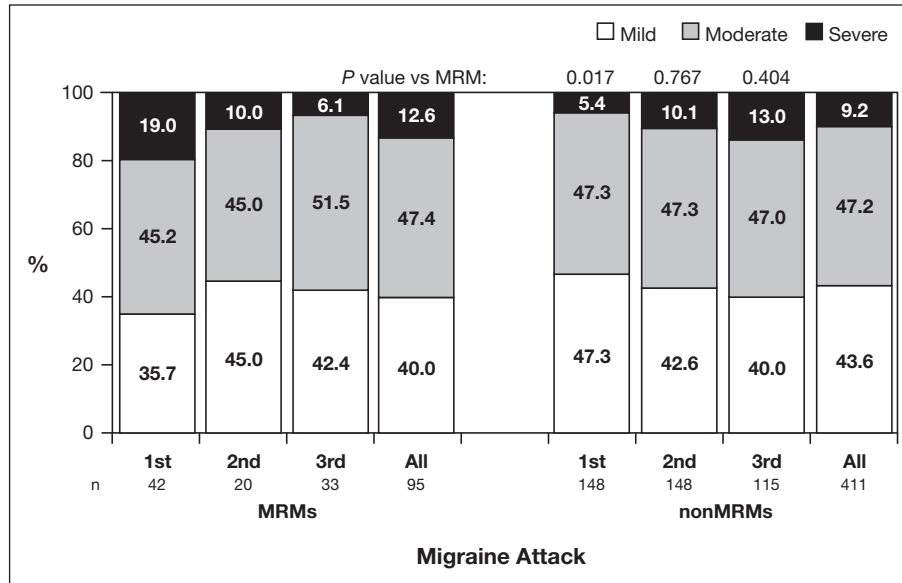


Fig 3.—Pretreatment level of pain intensity. Proportion of menstrually related migraines (MRMs) and nonmenstrually related migraines (nonMRMs) with mild, moderate, and severe pain intensity pretreatment for the first, second, third, and all attacks: combined treatment groups.

nonMRM in attack 1; for attacks 2 and 3, there were no statistically significant differences in overall level of functional disability between the MRM and nonMRM.

Efficacy of Almotriptan.—Almotriptan was similarly effective for the treatment of both MRM and

nonMRM (Fig. 5). In a pooled analysis of all migraine attacks, 2-hour pain-free rates of 35.4% vs 35.9%, 2-hour pain-relief rates of 77.4% vs 68.3%, and SPF rates of 22.9% vs 23.8% were reported for MRM vs nonMRM, respectively. In independent analyses of each of the 3 migraine attack groups, no statistically

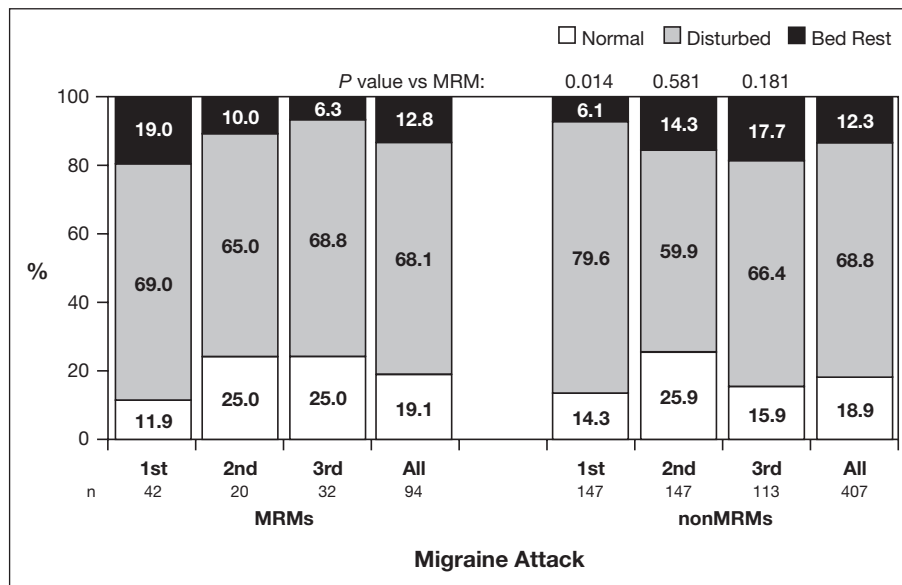


Fig 4.—Pretreatment level of functional disability. Proportion of menstrually related migraines (MRMs) and nonmenstrually related migraines (nonMRMs) with levels of function defined as normal, disturbed but can continue to work, and disturbed and bed rest required, pretreatment for the first, second, third, and all attacks: combined treatment groups.

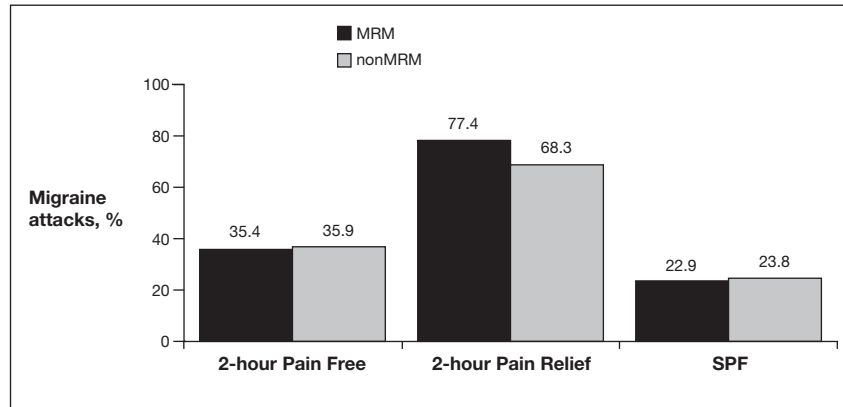


Fig 5.—Proportion of migraine attacks achieving 2-hour pain free, 2-hour pain relief, and sustained pain free (SPF) in the almotriptan-treatment group: all attacks combined. Two-hour pain free defined as a decrease in baseline pain intensity from severe, moderate, or mild, to no pain, without the use of supplemental pain medication and/or anti-emetic medication; 2-hour pain relief defined as a decrease in baseline pain intensity from severe or moderate to mild or no pain, without the use of supplemental pain medication and/or anti-emetic medication; SPF defined as pain free at 2 hours posttreatment with no recurrence of moderate or severe headache pain over the ensuing 2-24 hours, with no use of supplemental pain medication and/or no use of anti-emetic medication through 24 hours posttreatment.

significant differences were seen between MRM and nonMRM for any of the efficacy endpoints specified in the *post hoc* analyses (2-hour pain-free rates: 45.0% vs 39.0% for attack 1, 33.3% vs 33.3% for attack 2, 26.3% vs 35.2% for attack 3; 2-hour pain-relief rates: 78.6% vs 71.4% for attack 1, 100.0% vs 71.7% for attack 2, 66.7% vs 60.0% for attack 3; SPF rates: 25.0% vs 28.6% for attack 1, 22.2% vs 14.7% for attack 2, 21.1% vs 29.6% for attack 3, MRM vs nonMRM, respectively).

Almotriptan was also effective in providing relief from migraine-associated symptoms in both MRM and nonMRM (Table 2). In a pooled analysis of all migraine attacks, for both MRM and nonMRM, treatment with almotriptan resulted in a greater proportion of attacks that were free from the symptoms of phonophobia, photophobia, and nausea at 2 hours posttreatment compared with placebo treatment.

Treatment with almotriptan was associated with a greater proportion of attacks in which patients reported a return to normal level of function at 2 hours compared with placebo treatment for both MRM and nonMRM (Fig. 6). When comparisons were made between MRM and nonMRM, a normal level of function was reported in 56.5% of MRM attacks at 2 hours posttreatment with almotriptan compared with 14.9% pretreatment and a normal

level of function was reported in 46.7% of nonMRM attacks at 2 hours posttreatment with almotriptan compared with 16.3% pretreatment.

Paired Analyses.—A total of 83 patients (44 in the almotriptan-treatment group and 39 in the placebo-treatment group) had at least 1 MRM and 1 nonMRM during the trial. The demographic characteristics of this subgroup were similar to that of the total population. Paired analyses in this subgroup population corroborated the finding in the total population that almotriptan was similarly effective for the treatment of both MRM and nonMRM: 2-hour pain-free rates of 36.4% vs 40.9%, 2-hour pain-relief rates of 76.9% vs 73.1%, and SPF rates of 25.0% vs 18.2% were reported for MRM vs nonMRM, respectively. The paired analyses also showed that treatment with almotriptan was associated with a greater proportion of attacks in which patients reported a return to normal level of function at 2 hours compared with placebo treatment for both MRM and nonMRM and that almotriptan also was effective in providing relief from migraine-associated symptoms in both MRM and nonMRM.

Adverse Events.—In the total AEGIS evaluable for safety population (all randomized patients who took study medication and had postdose safety information, N = 347), the percentage of patients experi-

Table 2.—Presence of Migraine-Associated Symptoms Pretreatment and at 2 Hours Posttreatment

	MRM				nonMRM				
	Pretreatment	2 hours posttreatment	Change	Pretreatment	2 hours posttreatment	Change	Pretreatment	2 hours posttreatment	Change
Phonophobia, % patients	80.9	38.3	↓42.6	76.3	48.0	↓28.3	76.3	48.0	↓28.3
	Placebo	48.9	↓12.8	74.5	60.2	↓14.3	74.5	60.2	↓14.3
Photophobia, % patients	93.6	55.3	↓38.3	78.8	53.0	↓25.8	78.8	53.0	↓25.8
	Placebo	57.4	↓17.1	78.9	64.7	↓14.2	78.9	64.7	↓14.2
Nausea, % patients	40.4	23.4	↓17.0	39.9	30.2	↓9.7	39.9	30.2	↓9.7
	Placebo	27.7	↓12.7	27.0	25.9	↓1.1	27.0	25.9	↓1.1

MRM, menstrually related migraine; nonMRM, nonmenstrually related migraine.

encing any AE was 23.0% for almotriptan 12.5 mg and 23.7% for placebo.¹⁷ The percentage of patients experiencing ≥ 1 treatment-emergent (within 24 hours of drug dosing) AEs was 9.8% for almotriptan 12.5 mg and 6.4% for placebo. The treatment-emergent AEs that occurred with a frequency of $\geq 1\%$ in either treatment group (equivalent to ≥ 2 patients) were somnolence (1.1% and 2.3%), nausea (1.1% and 1.7%), vomiting (1.1% and 0.6%), and fatigue (1.1% and 0%), respectively, in almotriptan vs placebo treatment groups.

DISCUSSION

These *post hoc* analyses of data from a multicenter, randomized, double-blind, placebo-controlled trial demonstrated that the clinical characteristics of MRM, defined as migraine headaches occurring from 2 days before to 2 days after the first day of menstrual flow, are similar to nonMRM with regard to their association with aura, AAS, phonophobia, photophobia, nausea, level of pain intensity, and level of functional disability. In addition, almotriptan was similarly effective for the treatment of MRM and nonMRM as measured by efficacy outcomes that included 2-hour pain free, 2-hour pain relief, SPF, relief from migraine-associated symptoms, and return to normal function.

A limitation of this *post hoc* analysis was that it included all patients who reported ≥ 1 menses during the AEGIS trial. As the ICHD-2 diagnosis of MRM requires menstrual attacks in at least 2 out of 3 menstrual cycles and additionally at other times of the cycle, it is not clear if all of these women truly met the ICHD-2 criteria for MRM or if some may have had 1 migraine attack randomly associated with their menses.

While the pretreatment level of pain intensity was similar in a pooled analysis of all MRM and nonMRM attacks, in the first migraine attack group the level of pain intensity was significantly higher for MRM compared with nonMRM. There are conflicting historical data regarding the severity of pain intensity associated with MRM compared with nonMRM; this may be a consequence of the different variations of definitions for MRM used in studies of MRM. In this study, we defined MRM as those migraines occurring in the 5-day period from 2 days before to 2 days after the first

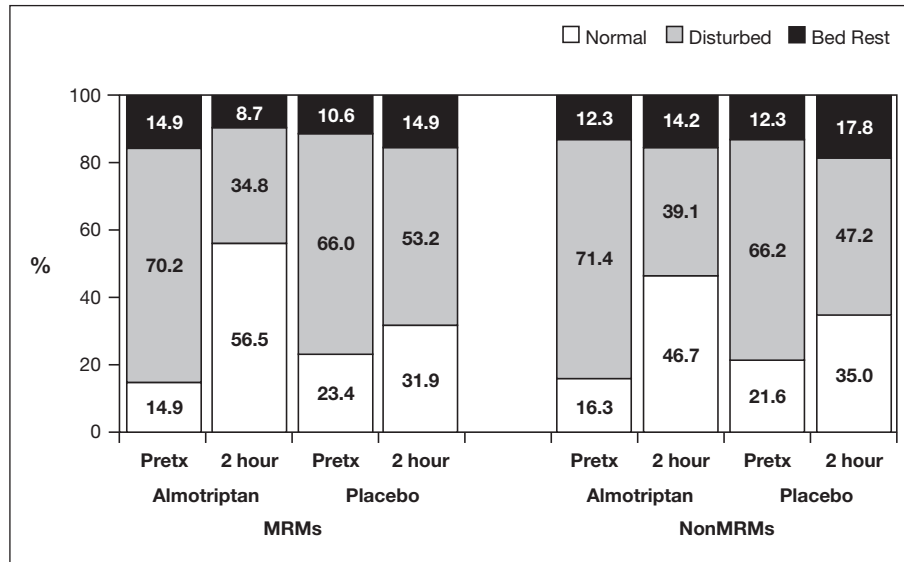


Fig 6.—Level of functional disability pretreatment and 2 hours posttreatment. Proportion of menstrually related migraines and nonmenstrually related migraines with levels of function defined as normal, disturbed but can continue to work, and disturbed and bed rest required, pretreatment (Pretx) and 2 hours posttreatment in the almotriptan-treatment group and the placebo-treatment group: all attacks combined.

day of menstrual flow. In comparison, a multivariate analysis by Granello et al, which evaluated MRM in 64 women referred to specialty headache centers, demonstrated that MRMs were associated with a significantly greater pain intensity but only for attacks occurring from the third to seventh day of the menstrual cycle vs nonmenstrual migraine attacks (migraines occurring from the eighth day of the menstrual cycle to 3 days before the onset of menstrual bleeding with the next cycle).⁸ In a study of 21 women recruited from a headache center who kept daily headache diaries, Martin et al reported that headache pain intensity was greater in the menstruation intervals (first to sixth day of the menstrual cycle) than in the mid-luteal intervals but was unchanged compared with the mid-cycle intervals.⁵ Stewart et al performed a prospective, population-based, daily diary study and concluded that while migraine headaches were significantly more painful during the first 2 days of the menstrual cycle, the magnitude of the differences were small.⁹ In migraine with aura there was an overall increase of 0.4 points in headache pain intensity scored on a 0-10 visual analog pain scale during the first 2 days of menses compared with the intensity of headache pain on all other days of the cycle; in migraine without aura the overall increase was 0.3 points. In the analyses

of headaches that occurred from 2 days before to the onset of menstrual flow, there was an overall reduction of 0.3 points in headache pain intensity in migraine with aura and an overall reduction of 0.2 points in migraine without aura. By analyzing only those migraines that occur in the first few days after the onset of menstrual flow when headache pain may be more severe and excluding migraines that occur in the days before the onset of menstrual flow, when headache pain may be less severe, the results of previous studies may not truly characterize the headache intensity of MRM pain as it is currently defined in the ICHD-2. Only MacGregor and Hackshaw, in their daily diary study of 155 women who were attending a migraine clinic, defined MRM as those migraines occurring ± 2 days of the onset of menstrual flow. Their findings demonstrated that women were more likely to have severe migraine on the first day of menstruation or during the following 2 days (relative risk 3.41) compared with other times of the menstrual cycle; results for the postmenstruation interval were highly significant and those for the premenstrual interval were also generally significant.⁴

In this current study, the pretreatment levels of functional disability were similar in attacks of MRM and nonMRM in a pooled analysis of all migraine

attacks, but in the first migraine attack group the level of functional disability was significantly greater for MRM compared with nonMRM. This finding could have been anticipated because the level of pain intensity was also greater for MRM in the first migraine attack group and pain severity was previously shown to be a correlate of functional disability.¹⁸ Disability has been variably defined in previous studies that evaluated the characteristics of MRM and, as described earlier, the time intervals used to define MRM have differed in these trials. Granella et al reported that migraine-related disability was greater in premenstrual migraine attacks (in the 2 days before the onset of menstrual bleeding) in terms of missed work hours and in menstrual migraine attacks (in the first 2 days of the menstrual cycle) in terms of lost work hour equivalents compared with nonmenstrual migraine attacks, although the authors indicated that they could not distinguish between work stoppage resulting from the migraine only and that which resulted from a premenstrual syndrome or menstruation itself.⁸ Martin et al reported that the disability index was greater in the menstrual intervals (first to sixth day of the menstrual cycle) than the disability index in the mid-luteal intervals; these findings are in agreement with this study's report of greater pain intensity levels in the menstrual intervals compared with the mid-luteal intervals.⁵ In contrast, Stewart et al reported no significant differences in disability scores at different times in the menstrual cycle.⁹ A survey questionnaire completed by 30 women at a health center investigated time lost and time spent at <50% productivity associated with migraines that occurred inside and outside of the menstrual period.¹⁹ The rank order of time lost was not significantly greater for migraine attacks taking place inside the menstrual period compared with those taking place outside of the menstrual period while the rank order of time at <50% productivity was significantly greater for attacks taking place inside vs outside the menstrual period.

In this current study, the presence of migraine-associated phonophobia, photophobia, and nausea before treatment were similar for attacks of MRM vs nonMRM in a pooled analysis of all migraine attacks. This finding is in agreement with the report of Granella et al.⁸

Almotriptan was similarly effective for the acute treatment of MRM and nonMRM as measured by efficacy outcomes that included 2-hour pain free, 2-hour pain relief, SPF, relief from migraine-associated symptoms, and return to normal function. While some trials have reported that menstrual migraines are more resistant to treatment,^{7,8} a number of other trials have found sumatriptan, zolmitriptan, rizatriptan, and almotriptan to be effective for the acute treatment of menstrual migraines.¹⁰⁻¹⁶

A subgroup analysis from a European trial reported that almotriptan and zolmitriptan were effective for the treatment of menstrual migraine, defined as migraine attacks occurring 2 days before to 4 days after the onset of menses.¹⁶ The large (N = 1061) multicenter, multinational, randomized, double-blind, parallel-group clinical trial, conducted at 118 centers in 9 European countries, evaluated the efficacy and tolerability of almotriptan 12.5 mg vs zolmitriptan 2.5 mg in the acute treatment of migraine.²⁰ A retrospective analysis of this trial included 902 women, 255 of whom treated a menstrual migraine attack (136 with almotriptan and 119 with zolmitriptan).¹⁶ No significant difference between the 2 treatments was found and these findings also did not appear to be different from the primary analysis which included all patients and all migraines. In the subgroup analysis of menstrual migraines, 2-hour pain relief was achieved by 67.9% of almotriptan-treated and 68.6% of zolmitriptan-treated patients, and 2-hour pain free was achieved by 44.9% and 41.2% of patients, respectively.¹⁶ This is comparable to the 2-hour pain-relief rates of 65.4% and 70.2% and the 2-hour pain-free rates of 43.5% and 48.3% reported for almotriptan and zolmitriptan, respectively, in the primary analysis of all patients.²⁰

In agreement with these data, results of this current study have demonstrated that almotriptan is more effective than placebo in the acute treatment of migraine attacks, relief from migraine-associated symptoms, and providing a return to normal functioning in both MRM and nonMRM.

In summary, this *post hoc* subgroup analysis of data obtained from women who reported ≥ 1 menses during the trial demonstrated that the pretreatment clinical characteristics of MRM and nonMRM were

similar. Almotriptan, a medication with proven efficacy in the acute treatment of migraine, is equally effective for the acute treatment of MRM. Almotriptan treatment was associated with an AE profile that was similar to placebo treatment.

REFERENCES

1. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache*. 2001;41:646-657.
2. Brandes JL. The influence of estrogen on migraine. *JAMA*. 2006;295:1824-1830.
3. Loder E, Rizzoli P, Golub J. Hormonal management of migraine associated with menses and the menopause: A clinical review. *Headache*. 2007;47:329-340.
4. MacGregor EA, Hackshaw A. Prevalence of migraine on each day of the natural menstrual cycle. *Neurology*. 2004;63:351-353.
5. Martin VT, Wernke S, Mandell K, et al. Defining the relationship between ovarian hormones and migraine headache. *Headache*. 2005;45:1190-1201.
6. International Headache Society. The international classification of headache disorders. 2nd edn. *Cephalalgia*. 2004;24(Suppl. 1):1-151.
7. Couturier EGM, Bomhof MAM, Neven AK, van Duijn NP. Menstrual migraine in a representative Dutch population sample: Prevalence, disability and treatment. *Cephalalgia*. 2003;23:302-308.
8. Granella F, Sances G, Allais G, et al. Characteristics of menstrual and nonmenstrual attacks in women with menstrually related migraines referred to headache centres. *Cephalalgia*. 2004;24:707-716.
9. Stewart WF, Lipton RB, Chee E, Sawyer J, Silberstein SD. Menstrual cycle and headache in a population sample of migraineurs. *Neurology*. 2000;55:1517-1523.
10. Facchinetti F, Bonellie G, Kangasniemi P, Pascual J, Shuaib A. The efficacy and safety of subcutaneous sumatriptan in the acute treatment of menstrual migraine: The Sumatriptan Menstrual Migraine study group. *Obstet Gynecol*. 1995;86:911-916.
11. Loder E, Silberstein SD, Abu-Shakra S, Mueller L, Smith T. Efficacy and tolerability of oral zolmitriptan in menstrually associated migraine: A randomized, prospective, parallel-group, double-blind, placebo-controlled study. *Headache*. 2004;44:120-130.
12. Landy S, Savani N, Shackelford S, Loftus J, Jones M. Efficacy and tolerability of sumatriptan tablets administered during the mild-pain phase of menstrually associated migraine. *Int J Clin Pract*. 2004;58:913-919.
13. Solbach MP, Waymer RS. Treatment of menstrually-associated migraine headaches with subcutaneous sumatriptan. *Obstet Gynecol*. 1993;82:769-772.
14. Silberstein SD, Massiou H, Le Jeunne C, Johnson-Pratt L, McCarroll KA, Lines CR. Rizatriptan in the treatment of menstrual migraine. *Obstet Gynecol*. 2000;96:237-242.
15. Dowson AJ, Massiou H, Aurora SK. Managing migraine headaches experienced by patients who self-report with menstrually related migraine: a prospective, placebo-controlled study with oral sumatriptan. *J Headache Pain*. 2005;6:81-87.
16. Allais G, Acuto G, Cabarrocas X, Esbri R, Benedetto C, Bussone G. Efficacy and tolerability of almotriptan versus zolmitriptan for the acute treatment of menstrual migraine. *Neurol Sci*. 2006;27(Suppl 2):S193-S197.
17. Mathew NT, Finlayson G, Smith TR, et al. Early intervention with almotriptan: Results of the AEGIS trial (AXERT[®] Early miGraine Intervention Study). *Headache*. 2007;47:189-198.
18. Freitag F, Smith T, Mathew N, et al. Effect of early intervention with almotriptan vs placebo on migraine-associated functional disability: Results from the AEGIS trial. *Headache*. doi:10.1111/j.1526-4610.2007.1044.x.
19. Dowson AJ, Kilminster SG, Salt R, Clark M, Bundy MJ. Disability associated with headaches occurring inside and outside the menstrual period in those with migraine: A general practice study. *Headache*. 2005;45:274-282.
20. Goadsby PJ, Massiou H, Pascual J, et al. Almotriptan and zolmitriptan in the acute treatment of migraine. *Acta Neurol Scand*. 2007;115:34-40.