

Review Article

Allodynia-Associated Symptoms, Pain Intensity and Time to Treatment: Predicting Treatment Response in Acute Migraine Intervention

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Objective.—To evaluate the relationship between treatment outcomes and allodynia-associated symptoms (AAS) at the time of treatment with almotriptan.

Methods.—Analyses were performed with data collected prospectively from patients in 2 recently completed early intervention trials, AXERT® Early miGraine Intervention Study (AEGIS) and AXERT® 12.5 mg time vs Intensity Migraine Study (AIMS): 2-hour pain free, 2-hour pain relief (AEGIS only), sustained pain free (SPF), use of rescue medication, and median headache duration (AIMS only), in the presence and absence of pretreatment AAS, which was determined by responses to a questionnaire. Analyses were conducted to evaluate possible prognostic variables.

Results.—The presence of pretreatment AAS did not have a significant effect on 2-hour pain-free, 2-hour pain-relief or SPF rates, use of rescue medication, or headache duration. Significant factors for most favorable outcomes (greater 2-hour pain-free, 2-hour pain-relief and SPF rates, less use of rescue medication, and shorter headache duration) included treatment with almotriptan 12.5 mg, treatment of mild or moderate headache pain, and treatment within 1 hour of headache onset.

Conclusion.—Almotriptan 12.5 mg was efficacious in providing 2-hour pain free, 2-hour pain relief, SPF, and reducing rescue medication use irrespective of the presence of AAS at the time of treatment. The most optimal efficacy outcomes occurred when patients treated migraine attacks early and before the onset of severe pain. The presence of AAS, which may indicate an early phase of allodynia, did not influence the efficacy of almotriptan therapy.

Key words: migraine, allodynia, almotriptan, early intervention

Abbreviations: AAS allodynia-associated symptoms, AEGIS AXERT® Early miGraine Intervention Study, AIMS AXERT® 12.5 mg time vs Intensity Migraine Study, ET early treatment, PDA personal digital assistant, SPF sustained pain free, ST standard treatment

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During their early clinical development and in the pivotal trials of all serotonin (5-HT) receptor_{1B/1D} agonists (triptans) for the acute treatment of migraine, the primary efficacy measure was headache relief (also called headache response), defined as a decrease in headache pain intensity from severe or moderate to mild or none. For this reason patients enrolled in these trials were instructed to administer the study drug when their headache pain was moderate to severe in intensity. More recent recommendations suggest that headache relief should still be measured, but as a secondary endpoint, mainly to enable comparison of the results of newer trials with those of the earlier ones.¹ A wide body of recent clinical experience now indicates that early treatment (ET) when migraine headache pain is mild may enable a more optimal therapeutic response, for

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example, achievement of 2-hour pain free and sustained pain free (SPF) outcomes.²⁻⁴

Retrospective analyses of clinical studies of acute migraine treatment with almotriptan 12.5 mg have demonstrated significantly greater 1-hour pain-free, 2-hour pain-free, and SPF rates, lower recurrence rates, and less use of rescue medication for patients who treated their migraine attacks when headache pain was mild compared with those who treated when headache pain intensity was moderate-to-severe.^{5,6} In addition, 2-hour pain-free and SPF rates were substantially better for patients who treated moderate-to-severe headaches within 1 hour of pain onset.⁷ Results consistent with these retrospective analyses were obtained in 2 prospective, randomized, early-intervention trials of almotriptan 12.5 mg.^{8,9} In the AXERT[®] Early miGraine Intervention Study (AEGIS), treatment with almotriptan 12.5 mg at the earliest onset of headache pain and no later than 1 hour after the migraine's onset resulted in significantly better 2-hour pain-free and SPF rates compared with placebo.⁸ In the AXERT[®] 12.5 mg time vs Intensity Migraine Study (AIMS), while both pretreatment headache pain intensity and time to treatment were significant predictors of treatment outcome, headache pain intensity at treatment initiation was a stronger predictor of 2-hour pain free and SPF, and time to treatment was a stronger predictor of headache duration and use of rescue medication.⁹ More recently, the randomized, double-blind, placebo-controlled "Act When Mild-AwM" study of almotriptan 12.5 mg treatment demonstrated greater 2-hour pain-free and SPF rates for patients who treated with almotriptan 12.5 mg when headache pain was mild and within 1 hour of headache onset, compared with those who took almotriptan 12.5 mg when their headache pain intensity was moderate-to-severe.¹⁰

The strategy for acute treatment of migraine that has been recommended has been termed "early intervention." Two differing definitions exist for early intervention. One involves initiating treatment early in the time course of an attack whereas the other involves initiating treatment when the intensity of headache pain is mild. Which of these is the optimal treatment strategy has been under considerable debate.

Furthermore, there are conflicting reports in the literature regarding the relationship between the presence of cutaneous allodynia and treatment outcome. Development of central sensitization and consequent cephalic cutaneous allodynia, in which normally non-noxious stimuli elicit painful sensations most typically in regions of the face, scalp, and ears,¹¹⁻¹³ may mark a point during the evolution of a migraine when pain and other symptoms of the attack become less responsive to triptan intervention. The repetitive occurrence of central sensitization with recurring migraine attacks has been proposed as a mechanism for the transformation of episodic migraine to forms of migraine with very frequent attacks (chronic migraine).¹¹

Whether the presence of allodynia supersedes both timing of therapy and pain intensity at the initiation of treatment as the main arbiter of therapeutic response is also a contentious issue that is not well understood.¹³⁻¹⁸ A growing body of data suggests that acute therapy may be effective for treating some patients who had already developed symptoms of cephalic cutaneous sensitivity at the time of treatment intervention.^{15-17,19}

Assessment of allodynia traditionally has been performed using quantitative sensory testing (QST), a technique for measuring pain thresholds that is often impractical for use in large clinical trials.^{20,21} More recent studies from several groups have used questionnaires to attempt to identify allodynic patients or those with symptoms of central sensitization.²⁰⁻²⁴ The objectives of the present analyses were to evaluate the relationship between the presence of allodynia-associated symptoms (AAS), as determined by responses to a questionnaire, with pain intensity at time of treatment and the time to treatment after headache onset on response to treatment with almotriptan 12.5 mg.

METHODS

Study Designs of the AEGIS and AIMS Trials.—The AEGIS trial was a multicenter, randomized, double-blind, parallel-group trial conducted at 37 centers in the United States in which patients were randomized in a 1:1 ratio to treat 3 consecutive migraine attacks with either almotriptan 12.5 mg or

matching placebo.⁸ All patients were given the same instructions, that is, to self-administer their study medication at the earliest onset of headache pain of any intensity, typical of their usual migraine, and no later than 1 hour after the migraine's onset, and to record their symptoms at multiple time points during their headaches using a personal digital assistant (PDA).

The AIMS trial was a multicenter, open-label, cluster-randomized study in which patients at 533 centers across the United States treated 2 sequential migraine headaches with almotriptan 12.5 mg.⁹ All patients at a treatment center (their cluster) treated with the same center-specified regimen, either ET, in which patients were instructed to self-administer almotriptan 12.5 mg at the earliest onset of migraine headache pain, which also was to be within 1 hour of the onset of the pain, or standard treatment (ST), when migraine pain intensity had become moderate or severe in intensity regardless of time from the onset of migraine headache pain. Patients were given a stopwatch to record headache duration and were instructed on how to complete a migraine assessment card and how to make the necessary telephone calls using an interactive voice response system to record symptoms at multiple time points during their headaches.

Patients Included in the AEGIS and AIMS Trials.—A comprehensive list of inclusion and exclusion criteria for the AEGIS and AIMS trials have been published previously.^{8,9} Key inclusion criteria for both trials were: patients 18-65 years of age with a history of International Headache Society-defined migraine of at least moderate pain intensity with or without aura for at least 1 year. In the AEGIS trial, patients were required to have had an average migraine headache frequency of 2-6 each month for the past 3 months. In the AIMS trial, patients were required to have had an average migraine headache frequency of 1-6 each month for the past 3 months. Key exclusion criteria for both trials were onset of migraine at >50 years of age or an average of ≥ 15 headache days/month in the previous 6 months. Patients were excluded if they had a contraindication to almotriptan or other triptan or previously discontinued almotriptan therapy because of an adverse

event (or a lack of efficacy in the AEGIS trial). The AIMS trial excluded patients who were, in the opinion of the investigator, treatment-refractory to triptans. Patients were excluded if they had migraine aura without headache or headaches that occurred predominantly upon awakening in the morning. The AEGIS trial excluded patients with routine nonmigraine headaches that would confound discrimination from migraine headache, hemiplegic or basilar migraine, or migraines typically accompanied by vomiting. Finally, patients in both trials were excluded for current, recent, or suspected history of substance dependence/abuse or chronic alcohol abuse within the past 6 months (or positive urine drug screen in the AEGIS trial).

Outcomes Measured in the AEGIS and AIMS Trials.—The primary efficacy outcome in the AEGIS trial was 2-hour pain free. The secondary efficacy outcomes included pain free at 0.5, 1, 4, and 24 hours; pain relief at 0.5, 1, 2, 4, and 24 hours; SPF; and use of rescue medication at 0-24 hours post-treatment. Two-hour pain free was 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 antiemetic medication at 2 hours postdose for the first headache. Pain relief was 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 antiemetic medication. SPF was defined as pain free at 2 hours postdose 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 antiemetic medication through 24 hours postdose.

The primary efficacy outcome in the AIMS trial was total headache duration, defined as the time from onset of headache pain until complete resolution of the migraine headache pain was achieved. Secondary efficacy outcomes included 2-hour pain free, SPF, and use of rescue medication before attaining pain free.

Both the AEGIS and AIMS trials assessed the presence of sensitization of pain sensory pathways and AAS using a 4-item questionnaire. Data from question 4, which was specific for symptoms suggestive of cephalic cutaneous sensitization (Do you have head or face pain or scalp tenderness in response to

touch or pressure that usually does not cause pain, such as wearing eyeglasses, combing your hair, wearing a hat, or lying down on the side that your headache is on?), were used to assess the presence of AAS.

Patients Included in Current Analysis.—In the AEGIS trial, of the 378 randomized patients (189 almotriptan, 189 placebo), 317 (162 almotriptan, 155 placebo) were included in the evaluable-for-efficacy population, defined as all patients who took study medication to treat the first qualifying migraine headache and had baseline and 2-hour post-treatment headache pain intensity data. Two patients in the almotriptan-treated group had incomplete AAS data and were not included in the current analysis (160 almotriptan, 155 placebo).

The AIMS trial enrolled 1268 patients in the ET group, and 757 of these patients were included in the evaluable-for-efficacy population, defined as all patients who took study medication and had information for their first headache pertaining to either duration of headache pain or time to rescue medication before achieving pain free; 1175 patients were enrolled in the ST group, 693 patients with a first headache who were included in the evaluable-for-efficacy population. Because of the overlap between ST patients who treated early and those in the ET cohort, comparative subgroup *post hoc* analyses were performed on several cohorts: ET patients who treated their mild, moderate, or severe migraine within 1 hour of pain onset ($ET \leq 1$ hour, $n = 652$), ST patients who treated their moderate or severe migraine within 1 hour of pain onset ($ST \leq 1$ hour, $n = 288$), and ST patients who treated their moderate or severe migraine greater than 1 hour from onset of pain ($ST > 1$ hour, $n = 364$). The ET patients who treated their migraine headache after 1 hour of pain onset ($n = 105$) and the ST patients who treated mild headache pain ($n = 41$) were excluded from the evaluable-for-efficacy populations and were not included in these *post hoc* analyses. Two patients (one in the $ST \leq 1$ hour subgroup and one in the $ST > 1$ hour subgroup) had incomplete AAS data and were excluded from the current analysis (287 patients in the $ST \leq 1$ hour subgroup, 363 patients in the $ST > 1$ hour subgroup).

Statistical Analyses.—All inferential statistical tests were 2-tailed and employed a type I error of 0.05. No corrections were made for multiplicity. Summaries and analyses presented here were based on the first study migraine headache for AEGIS or AIMS using the evaluable-for-efficacy populations.

In the AEGIS trial, the percentage of patients who achieved pain free, pain relief, and SPF were compared between treatment groups using a Cochran-Mantel-Haenszel general association test, stratified by pretreatment pain intensity and pooled center. The chi-square test was used to compare the proportion of patients with rescue medication usage between treatment groups.

In the AIMS trial, the statistical analyses, which accounted for the cluster-randomized study design, were conducted under a working correlation structure of independence among patients. The statistical sets of analyses for the dichotomous outcome results of 2-hour pain free and use of rescue medication were performed with Generalized Estimating Equation methodology using Proc GENMOD from version 9.1 of SAS (SAS Institute Inc., Cary, NC, USA). For the 2-hour pain-free variable, patients were assumed not to have a successful response if they required rescue medication within the first 2 hours. For each dichotomous variable, the comparative results of the groups were summarized by the odds ratio. The statistical sets of analyses for the duration of headache pain were performed using a proportional hazards model with treatment group only. To account for correlated observations of patients within an investigator, PROC SURVIVAL from the statistical program SUDAAN (Research Triangle Institute, Research Triangle Park, NC, USA) was utilized with investigator as the cluster. Patients who did not achieve initial complete pain free and re-medicated with study medication or took rescue medication were assigned a value of 24 hours for headache duration.

Analyses conducted to evaluate possible prognostic variables in the AEGIS trial included treatment group (placebo vs almotriptan), pretreatment headache pain intensity (mild and moderate vs severe), and pretreatment AAS (present vs absent; indicated by yes vs no response to question 4 of Central Sensitization Questionnaire-4). In the AIMS

ET population cohort, the analyses were conducted to evaluate baseline pain intensity (moderate vs severe) and pretreatment AAS (present vs absent). In the AIMS ST population cohort, analyses were conducted to evaluate as possible prognostic variables the baseline pain intensity (moderate vs severe), time to study medication administration (≤ 1 hour vs > 1 hour from headache onset), and pretreatment AAS (present vs absent).

RESULTS

Effect of AAS on Primary and Secondary Outcomes in AIMS and AEGIS.—In both the AEGIS and AIMS trials, the presence vs absence of pretreatment AAS did not have a significant effect on the proportion of patients who achieved 2-hour pain free (Fig. 1). When stratified by pretreatment pain intensity, patients who treated severe pain in the presence of AAS achieved the lowest 2-hour pain-free rates, but these were not significantly lower compared with the absence of AAS (Table 1). Two-hour pain-free rates in patients with pretreatment mild or moderate pain in the absence of AAS compared with severe pain in the presence of AAS were 34.7% vs 13.3% in the almotriptan-treated AEGIS population, 42.1% vs 28.0% in the ET ≤ 1 hour AIMS population, 51.8% vs 15.8% in the ST ≤ 1 hour AIMS population, and 43.0% vs 22.4% in the ST > 1 hour AIMS population. A similar result was seen for 2-hour pain relief in data collected in the AEGIS trial (the AIMS trial did not collect data on this endpoint), that is, the presence vs absence of AAS did not have a significant effect on the proportion of patients who achieved 2-hour pain relief (Fig. 2, Table 1).

The proportion of patients who achieved SPF was greater in patients without pretreatment AAS compared with those with pretreatment AAS in both the AEGIS and AIMS trials (Fig. 3). This pattern continues when patients are stratified by pretreatment headache pain intensity (Table 1). Sustained pain-free rates in patients with pretreatment mild or moderate pain in the absence of AAS compared with severe pain in the presence of AAS were 30.6% vs 6.7% in the almotriptan-treated AEGIS population, 19.7% vs 6.9% in the ET ≤ 1 hour AIMS population,

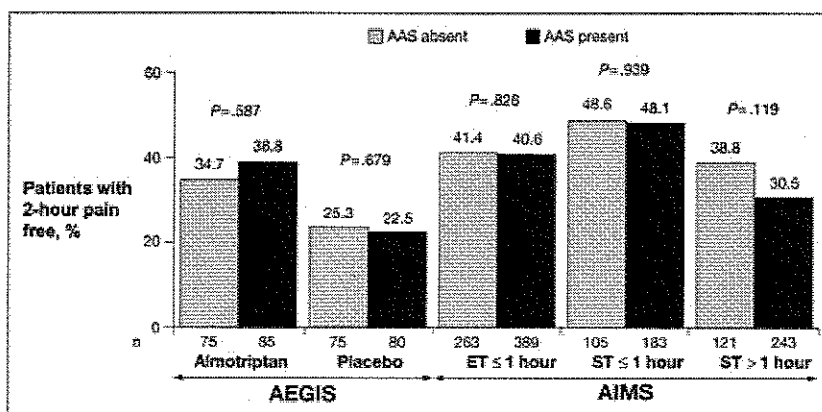


Fig 1.—Proportion of patients achieving 2-hour pain free relative to presence vs absence of pretreatment allodynia-associated symptoms (AAS). AEGIS = AXERT® Early miGraine Intervention Study; AIMS = AXERT® 12.5 mg time vs Intensity Migraine Study; ET = early treatment; ST = standard treatment.

28.6% vs 6.7% in the ST ≤ 1 hour AIMS population, and 17.6% vs 4.9% in the ST > 1 hour AIMS population.

Use of rescue medication was measured differently in the 2 trials: in AEGIS, use of rescue medication was measured from 0 to 24 hours post-treatment whereas in AIMS, it was defined as use any time before attaining pain free. In both the AEGIS and AIMS trials, the proportion of patients using rescue medication was substantially lower in patients without pretreatment AAS compared with those with pretreatment AAS (Fig. 4). This pattern continued after stratification by pretreatment headache pain intensity (Table 1) with lower use of rescue medication in patients with pretreatment mild or moderate pain in the absence of AAS compared with severe pain in the presence of AAS: 36.1% vs 46.7% in the almotriptan-treated AEGIS population, 30.8% vs 56.0% in the ET ≤ 1 hour AIMS population, 9.7% vs 34.2% in the ST ≤ 1 hour AIMS population, and 45.2% vs 64.2% in the ST > 1 hour AIMS population.

Headache duration, the primary endpoint of the AIMS trial but not measured in the AEGIS trial, was unaffected by the presence of AAS in the subgroups that treated early (ET ≤ 1 hour and ST ≤ 1 hour), but was substantially longer in patients with pretreatment AAS in the subgroup of patients who treated later (ST > 1 hour) (Fig. 5). The effect of pretreatment pain intensity and presence vs absence of AAS on headache duration is shown in Table 2.

Evaluation of Prognostic Variables.—Evaluation of prognostic variables in the AEGIS trial (Table 3) showed that assignment to almotriptan vs placebo was the strongest predictor of superior outcomes. Mild or moderate pain intensity pretreatment compared with severe pain intensity pretreatment was also a predictor of significantly better 2-hour pain-free and 2-hour pain-relief rates and had some impact on the SPF rate. Pretreatment AAS was not a significant predictor of the 4 outcomes measured.

Evaluation of the prognostic variables in the ET arm of AIMS showed that mild or moderate migraine headache pain intensity as compared with severe pain intensity at the time of treatment was predictive for superior primary (shorter headache duration) and secondary (greater 2-hour pain-free and SPF rates, less use of rescue medication) outcomes (Table 4). Pretreatment AAS was not a significant predictor of the 4 outcomes measured. In the ST arm, both pretreatment moderate headache pain intensity as compared with severe pain intensity and treatment at earlier time points (≤ 1 hour vs > 1 hour) were associated with superior primary and secondary outcomes. For 2-hour pain free and SPF, headache pain intensity (ie, moderate vs severe) was a stronger predictor of superior outcomes than time to treatment (ie, ≤ 1 hour vs > 1 hour). For headache duration and use of rescue medication, time to treatment was a better predictor compared with pretreatment headache pain intensity. Pretreatment AAS was not a significant pre-

Table 1.—Effect of Pretreatment Headache Pain Intensity on Various Efficacy Endpoints in the Presence and Absence of AAS

Trial	AEGIS				AIMS					
	Almotriptan		Placebo		ET ≤ 1 hour		ST ≤ 1 hour		ST > 1 hour	
Treatment group	AAS-	AAS+	AAS-	AAS+	AAS-	AAS+	AAS-	AAS+	AAS-	AAS+
No. of patients	75	85	75	80	263	389	104	183	120	243
2-hour pain free, %	25/72 (34.7)	31/70 (44.3)	19/72 (26.4)	17/71 (23.9)	93/221 (42.1)	130/289 (45.0)	48/93 (51.8)	82/145 (56.6)	40/93 (43.0)	59/176 (33.5)
P value	.303		.848		.476		.498		.129	
Severe	1/3 (33.3)	2/15 (13.3)	0/3 (0)	1/9 (11.1)	16/42 (38.1)	28/100 (28.0)	3/11 (27.3)	6/38 (15.8)	7/27 (25.9)	15/67 (22.4)
P value	.442		1.000		.207		.366		.694	
2-hour pain relief, % (by definition, excluded patients who treated mild pain)										
Moderate	29/36 (80.6)	27/38 (71.1)	23/43 (53.5)	21/40 (52.5)						
P value	.402		1.000							
Severe	2/3 (67.7)	9/15 (60.0)	0/3 (0)	2/9 (22.2)						
P value	1.000		1.000							
Sustained pain free, %										
Mild/moderate	22/72 (30.6)	17/70 (24.3)	15/72 (20.8)	9/71 (12.7)	41/208 (19.7)	52/272 (19.1)	24/84 (28.6)	27/130 (20.8)	15/85 (17.6)	18/166 (10.8)
P value	.455		.263		.873		.196		.136	
Severe	0/3 (0)	1/15 (6.7)	0/3 (0)	1/9 (11.1)	5/37 (13.5)	6/87 (6.9)	1/9 (11.1)	2/30 (6.7)	3/23 (13.0)	3/61 (4.9)
P value	1.000		1.000		.234		.457		.176	
Use of rescue medication†, %										
Mild/moderate	26/72 (36.1)	31/70 (44.3)	42/72 (58.3)	45/71 (63.4)	68/221 (30.8)	86/289 (29.8)	9/93 (9.7)	27/145 (18.6)	42/93 (45.2)	86/176 (48.9)
P value	.392		.608		.808		.087		.569	
Severe	0/3 (0)	7/15 (46.7)	3/3 (100)	4/9 (44.4)	17/42 (40.5)	56/100 (56.0)	2/11 (18.2)	13/38 (34.2)	15/27 (55.6)	43/67 (64.2)
P value	.245		.205		.081		.357		.377	

† Defined as use of rescue medication from 0 to 24 hours post treatment in the AEGIS trial and as use of rescue medication before attaining pain free in the AIMS trial. AAS = allodynia-associated symptoms; AEGIS = AXERT® Early miGraine Intervention Study; AIMS = AXERT® 12.5 mg time vs Intensity Migraine Study; ET = early treatment; ST = standard treatment.

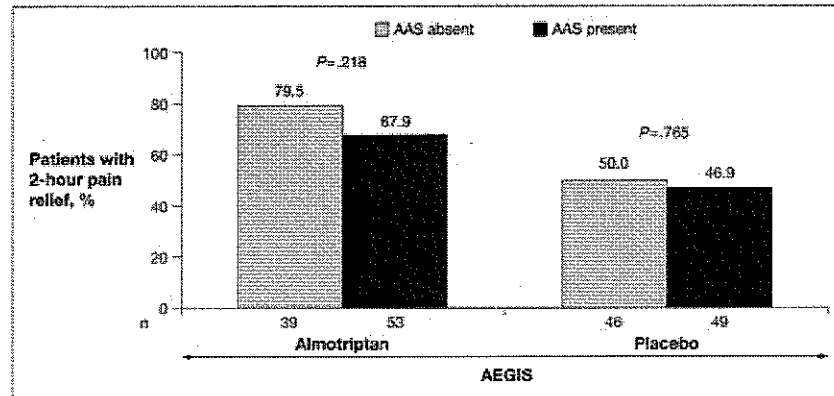


Fig 2.—Proportion of patients achieving 2-hour pain relief relative to presence vs absence of pretreatment allodynia-associated symptoms (AAS). AEGIS = AXERT® Early miGraine Intervention Study.

dictor of headache duration or 2-hour pain free, but was a significant predictor of SPF and had some impact on the use of rescue medication.

Evolution of AAS Post-treatment.—Figure 6 depicts the proportion of patients who reported AAS at designated time points before and after treatment with almotriptan or placebo. Within 1 hour after treatment, a similar proportion of patients in the 2 treatment groups were experiencing AAS. By 2 hours, fewer patients in the almotriptan-treated group compared with the placebo-treated group reported experiencing AAS; the difference between the almotriptan-treated and placebo-treated patients reporting AAS was significant at 4 and 24 hours post-treatment.

DISCUSSION

The development of triptans has been a major advance in the acute treatment of migraine headache,²⁵ but investigation of migraine treatment effectiveness and migraine pathophysiology continues.²⁶ The present analyses aimed to address a key clinical issue in the acute management of migraines: Is there an interaction between AAS and 2 treatment strategies with triptans: (1) treat when headache pain is mild; (2) treat early after migraine onset?

In the AEGIS and AIMS trials, patients receiving almotriptan 12.5 mg within 1 hour of headache onset demonstrated relatively high rates of 2-hour pain free independent of the presence or absence of AAS at the time of initial treatment. The combination of

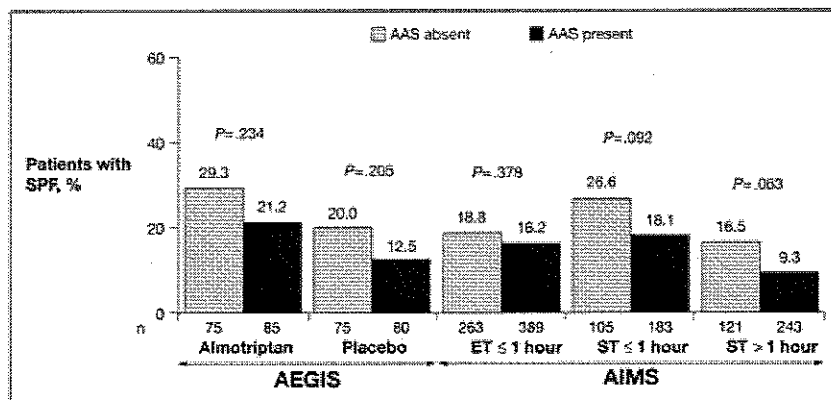


Fig 3.—Proportion of patients achieving sustained pain free (SPF) relative to presence vs absence of pretreatment allodynia-associated symptoms (AAS). AEGIS = AXERT® Early miGraine Intervention Study; AIMS = AXERT® 12.5 mg time vs Intensity Migraine Study; ET = early treatment; ST = standard treatment.

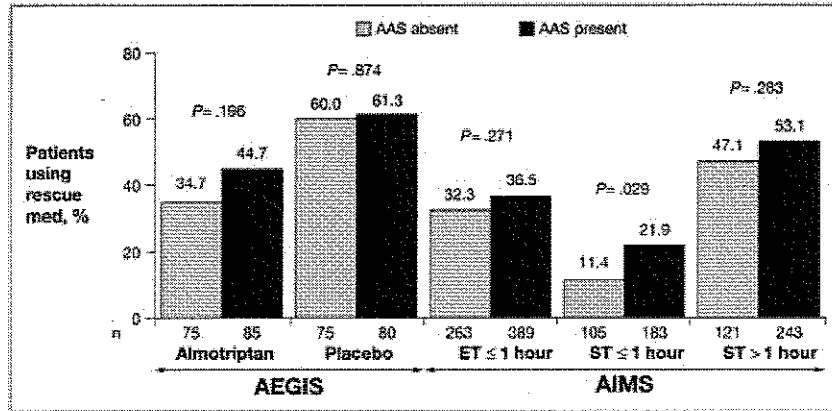


Fig 4.—Proportion of patients using rescue medication relative to presence vs absence of pretreatment allodynia-associated symptoms (AAS). AEGIS = AXERT® Early miGraine Intervention Study; AIMS = AXERT® 12.5 mg time vs Intensity Migraine Study; ET = early treatment; ST = standard treatment.

treatment delay (>1 hour after onset) and the presence of AAS was associated with a longer median headache duration in the AIMS trial; AAS in patients treating early (<1 hour) did not appear to affect headache duration. Treatment with almotriptan 12.5 mg was associated with significant reductions in the proportion of patients with post-treatment AAS at 4 and 24 hours compared with placebo treatment in the AEGIS trial. Significant factors for optimal treatment outcomes (besides almotriptan therapy) included treatment when headache pain intensity was mild or moderate, and timing of initial treatment within 1 hour of headache onset. The only influence of AAS observed was on SPF rate and use of rescue medication in the ST arm of the AIMS trial.

The benefits of treating migraine with a triptan early after onset and/or before the onset of moderate-to-severe headache pain have been demonstrated in numerous retrospective analyses and clinical studies of almotriptan 12.5 mg and other triptans.^{2,3,5-10,27-33} Findings for treatment of migraine with an oral triptan when cutaneous allodynia is present are more limited; these studies, specifically using oral forms of sumatriptan and rizatriptan, have suggested that the presence of cutaneous allodynia marked a clinically significant point in the progression of a migraine attack during which the triptans were less effective for managing migraine headache pain.^{13,21,34}

Triptans are generally believed to have their primary action on presynaptic 5-HT_{1B} receptors, on

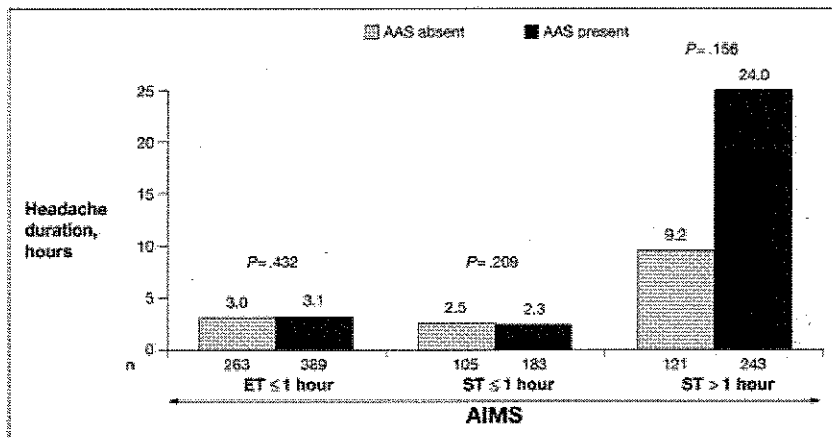


Fig 5.—Headache duration relative to presence vs absence of pretreatment allodynia-associated symptoms (AAS). AIMS = AXERT® 12.5 mg time vs Intensity Migraine Study; ET = early treatment; ST = standard treatment.

Table 2.—Effect of Pretreatment Headache Pain Intensity on Median Headache Duration (Hours) in the Presence and Absence of AAS: AIMS

Treatment group		ET ≤ 1 hour		ST ≤ 1 hour		ST > 1 hour	
		AAS–	AAS+	AAS–	AAS+	AAS–	AAS+
Presence of AAS							
No. of patients		263	389	104	183	120	243
Pretreatment pain intensity	Mild + moderate	3.00	2.60	–	–	–	–
	<i>P</i> value		.329				
	Moderate	–	–	2.33	2.08	8.00	18.5
	<i>P</i> value				.979		.125
	Severe	3.46	24	11.35	5.88	24	24
	<i>P</i> value		.092		.981		.446

AAS = allodynia-associated symptoms; AIMS = AXERT® 12.5 mg time vs Intensity Migraine Study; ET = early treatment; ST = standard treatment.

first-order meningeal nociceptive perivascular neurons, and on 5-HT_{1D} receptors on trigeminovascular fiber endings,³⁵ which might explain the enhanced efficacy of triptans for the relief of migraine pain when treatment is initiated early in a migraine attack while the migraine pain is primarily thought to be associated with peripheral nociceptive mechanisms such as trigeminovascular inflammation and peripheral sensitization. The findings of a reduction in pain relief responses to oral triptans after the development

of cutaneous allodynia (ie, a clinical marker for central sensitization) appear to be consistent with a hypothesis that 5-HT_{1B/1D} receptors are not expressed on the central nociceptive neurons of the spinal and medullary dorsal horn and other central structures.¹⁵

Burstein and colleagues, however, proposed another aspect of central sensitization that may be clinically relevant for the treatment of migraine after development of allodynia. They describe 2 functionally and anatomically distinct phases of central sensi-

Table 3.—Multivariate Evaluation of Prognostic Variables: AEGIS†

Efficacy endpoint	Prognostic variable	Risk ratio	<i>P</i> value
2-hour pain free	Treatment group	0.51	.0080
	Headache pain intensity	3.54	.0250
	AAS	1.16	.5660
2-hour pain relief	Treatment group	0.31	.0003
	Headache pain intensity	2.75	.0210
	AAS	0.85	.6120
SPF	Treatment group	0.55	.0390
	Headache pain intensity	3.78	.0780
	AAS	0.68	.1770
Use rescue medication 0-24 hours	Treatment group	2.32	.0003
	Headache pain intensity	1.16	.7050
	AAS	1.29	.2780

†Model included treatment group (placebo vs almotriptan), pretreatment headache pain intensity (mild and moderate vs severe), and pretreatment AAS (present vs absent).

AAS = allodynia-associated symptoms; AEGIS = AXERT® Early miGraine Intervention Study; SPF = sustained pain free.

Table 4.—Multivariate Evaluation of Prognostic Variables: AIMS†

Efficacy endpoint		Prognostic variable	Risk ratio	P value
ET population				
1	Headache duration	Headache pain intensity	1.77	<.001
		AAS	0.99	.955
2	2-hour pain free	Headache pain intensity	1.73	.011
		AAS	0.98	.911
	SPF	Headache pain intensity	2.61	.005
		AAS	1.12	.605
Use rescue medication	Headache pain intensity	2.41	<.001	
	AAS	1.10	.574	
ST population				
1	Headache duration	Headache pain intensity	1.70	<.001
		Time to treatment	2.80	<.001
		AAS	0.86	.163
2	2-hour pain free	Headache pain intensity	2.77	<.001
		Time to treatment	1.76	.001
		AAS	1.17	.418
	SPF	Headache pain intensity	2.62	.021
		Time to treatment	1.78	.020
		AAS	1.67	.033
Use rescue medication	Headache pain intensity	1.91	.007	
	Time to treatment	4.71	<.001	
	AAS	1.45	.071	

†Model included pretreatment headache pain intensity (moderate vs severe), time to treatment (≤ 1 hour vs >1 hour), and pretreatment AAS (present vs absent).
 AAS = allodynia-associated symptoms; AIMS = AXERT® 12.5 mg time vs Intensity Migraine Study; ET = early treatment; SPF = sustained pain free; ST = standard treatment.

tization: an initiation (or development) phase in which the clinical phenomena of central sensitization are dependent on primary afferent signals from meningeal nociceptors, and a maintenance phase in which the neuronal activities associated with central sensitization no longer require input from the periph-

eral afferents.^{12,13} Progression to the maintenance phase of allodynia, the more advanced stage of central sensitization, is believed to take up to 4 hours.¹³

Although these trials did not objectively confirm allodynia with QST, the presence of AAS reported by

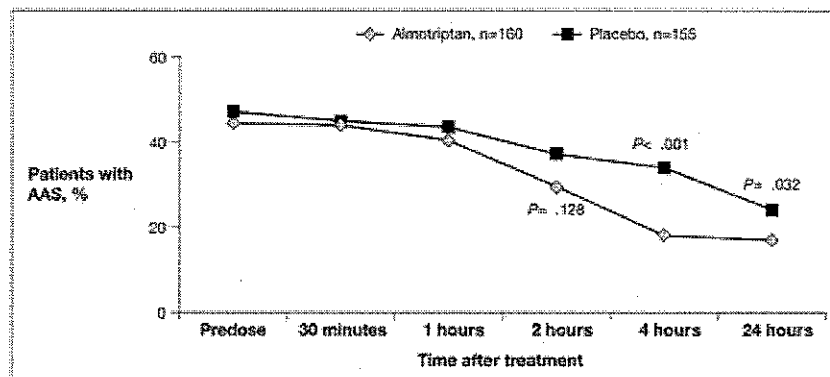


Fig 6.—Presence of allodynia-associated symptoms (AAS) pretreatment and 0.5, 1, 2, 4, and 24 hours post-treatment.

patients soon after the onset of the attack and when pain intensity was still mild may have been representative of the initiation phase of central sensitization. The timing of treatment in the AIMS trial was more consistent with the initiation phase than the maintenance phase of central sensitization, with a median time-to-treatment of 10 minutes after migraine onset in the ET arm and a median of 90 minutes in the ST arm.⁹ Treatment with a triptan during this early period, potentially before the progression to a maintenance phase of central sensitization, may underlie the preservation of efficacy recorded by patients who experienced AAS at the time of treatment with almotriptan 12.5 mg in the AEGIS and AIMS trials.

This interpretation is supported by the significant prognostic influence of time to treatment and headache pain severity at the time of treatment. In addition, the presence or absence of AAS appears to exert little influence on treatment outcomes when patients treated early or mild pain; however, the presence of AAS appears to have a negative relationship with treatment outcomes in patients who delayed treatment or treated when pain intensity was severe. A smaller influence of allodynia on outcomes was reported by Schoenen et al in a study comparing oral almotriptan with and without aceclofenac for treatment of moderate-to-severe migraine. In this trial, more severe headache intensity at baseline was associated with significantly lower efficacy; the presence of brush allodynia (assessed by the patient with a 2-cm brush) tended to decrease treatment response, but the effect was not statistically significant.¹⁹

A recent study demonstrated that patients who had developed cutaneous allodynia and who had a history of nonresponsiveness to oral triptans, reported high response rates for 2-hour pain free and SPF after treatment with subcutaneous sumatriptan 6 mg.¹⁷ The authors hypothesized that there is a time frame in which triptans may retain their effectiveness for the acute treatment of migraine in patients who have developed cutaneous allodynia, and that the time frame is longer (eg, 2 hours) for an injectable triptan than for an oral triptan (1 hour). A more recent study enrolling nonresponders to sumatriptan 100 mg observed a significant decrease in the mean visual analog scale score for pain 1 hour after treat-

ment with zolmitriptan nasal spray 5 mg during early allodynia.¹⁶ The positive results obtained in these studies may be related to Burstein et al's 2-phase hypothesis (initiation then maintenance)^{12,13} of the progressive development of central sensitization during a migraine attack, as discussed earlier. The differences in pharmacokinetic properties of oral and nonoral triptans may underlie the observed disparity in the efficacy of these 2 delivery forms of triptans for the treatment of migraine with AAS.

Studies that have reported positive results for acute triptan therapy in migraineurs with symptoms of central sensitization tended to be larger than the trials that reported negative results. In addition, the positive trials typically used questionnaires rather than QST to identify patients with symptoms of central sensitization and assessed these symptoms at the time of ET, before the probability of progression to the maintenance phase of central sensitization. For example, the 2 rizatriptan Treat A Migraine Early trials, which evaluated outcomes in 1030 patients, observed similar 2-hour pain-free rates for patients who treated with rizatriptan 10 mg within 1 hour of migraine onset irrespective of the presence or absence of baseline symptoms suggesting cephalic cutaneous sensitivity (assessed with a questionnaire).¹⁵

The size of the AIMS and AEGIS trials used in this *post-hoc* analysis precluded the use of QST and so a limitation of this analysis is that it relies on patient-reported symptoms rather than objective confirmation. Patients with AAS were identified in these trials by using a question that covers multiple manifestations associated with cephalic cutaneous allodynia. The use of questionnaires to identify patients with allodynia is becoming more common in the research arena.^{15,20-24} A validated Allodynia Symptom Checklist²³ was published after the AIMS and AEGIS studies were started.

Further data on the efficacy of almotriptan for the acute treatment of migraine in patients who experience AAS will be warranted to confirm these results. Relief of AAS should be an important goal of acute migraine treatment because AAS generally increase the disability of migraine attacks as it may interfere with normal activities of daily living such as

grooming and is often associated with greater pain intensity. Furthermore, recurrent events of central sensitization over time may be linked to the development of chronic migraine,^{11,36} although the effect of medications that prevent migraine or provide relief of migraine-associated AAS on this transformation process is unknown.

In summary, the results of these analyses of data from the AEGIS and AIMS trials demonstrated the efficacy of almotriptan 12.5 mg for providing 2-hour pain free, 2-hour pain relief, SPF, and reducing rescue medication use. The presence of pretreatment AAS, which may indicate an early phase of allodynia, did not have a substantial influence on almotriptan efficacy for the treatment of these attacks. The most optimal efficacy outcomes occurred when patients treated migraine attacks early in the attack and before the onset of severe pain.

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