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EXPERT REVIEW

Almotriptan Malate: Early Treatment in Acute Migraine

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Abstract: Almotriptan is a selective serotonin agonist used for the relief of moderate to severe migraine headaches. Clinical trials have begun to evaluate its use in the 'early' treatment of migraines, described as when a triptan is administered within 1 hour of the onset of headache for mild pain. These trials have demonstrated higher pain-free rates, decreased recurrence of migraines, and a reduction in the need for rescue medication compared to when the treatment is delayed until the pain is moderate to severe in intensity or beyond 1 hour of headache onset. Tolerability and safety of almotriptan for 'early' use is similar to standard administration of the medication.

Keywords: almotriptan, migraine, early treatment

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Introduction

Migraine is a common primary headache disorder characterized by recurrent episodes that may be disabling.[1] It is classified into six subtypes with two major subtypes being migraine with aura and migraine without aura.[1] Diagnosis is similar except that migraine with aura has a prodrome which includes reversible, focal neurological symptoms prior or at onset of the migraine. The aura usually develops over 5 to 20 minutes and lasts no longer than 60 minutes.[1]

Migraines occur in approximately 15%–18% of females and 6%–8% of males in Europe and the United States.[2,3] Central and South America have similar rates.[2] Migraines are diagnosed more commonly in Caucasian than African Americans.[3] The prevalence increases from 12 years of age until age 40 and then decreases,[4] with those ages 35 to 45 affected the most.[2] Migraines result in missed work or school, decreased productivity, and physical impairment in activities. It is ranked as 19th amongst all causes of years lived with disabilities.[2] Appropriate diagnosis and acute therapies are imperative for migraine treatment.

Non-pharmacologic and pharmacologic treatment options are available for the acute treatment of migraines. Of the pharmacologic options, 'triptans' are a first line agent recommended for moderate to severe migraines or when mild to moderate migraines do not respond to non-prescription medications.[5] Almotriptan is one of seven drugs that belong to the class called 'triptans.' Almotriptan (Axert® in the United States/Almogran® in Europe) is approved for the acute treatment of migraine with or without aura in adults. In the United States, it gained approval for migraine headache pain in adolescents (≥12 to 17 years of age) who have migraine with or without aura and who have attacks lasting 4 hours or longer.[6] Almotriptan is obtainable in 15 countries around the world. It is available in a 6.25 mg and 12.5 mg oral tablet with initial dosing ranging from 6.25 to 12.5 mg. A dose may be repeated two hours after the first dose if the headache returns, with a maximum daily dose of 25 mg.

Although the triptans have been recommended for use in moderate to severe migraine, clinical trials have evaluated various triptans for 'early' treatment of migraines. 'Early' treatment has a time and intensity component. 'Early' is described as when a triptan is administered within 1 hour of the onset of headache for mild pain from the migraine and not delaying administration until pain is described as moderate to severe. These trials have demonstrated higher pain-free rates, decreased recurrence of migraines, and reduction in the need for rescue medication.[7] However, weaknesses in trial design and evaluation as well as differences in defining the 'early' time period may limit these studies. This article will focus on the clinical data related to the use of almotriptan in the 'early' treatment of migraine headaches.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Almotriptan is a selective serotonin agonist (5-HT_{1B} and $_{1D}$) in the cranial arteries. It produces vasoconstriction, inhibits neuropeptide release, and decreases transmission in the trigeminal pain pathways.[6] Almotriptan is metabolized by monoamine oxidase (MAO) type A oxidative deamination (~27% of dose) to an indoleacetic acid metabolite and by the cytochrome P450 isoenzymes 2D6 and 3A4 (~12% of dose) to an intermediate that is further oxidized by aldehyde dehydrogenase to the gamma-aminobutyric acid derivative. Both metabolites are inactive. Flavin monooxygenase is a minor metabolic pathway.

Almotriptan is well absorbed with 70% bioavailability and may be administered without regards to food.[6] It has a peak plasma time of 1 to 3 hours. Almotriptan has only 35% protein bounding and the volume of distribution is approximately 180 to 200 L. The elimination half-life is 3 to 4 hours and it is excreted primarily in the urine with 40% of the drug unchanged. A small amount (~13%) is excreted in the feces as metabolites and unchanged drug. Almotriptan should be used with caution in patients with hepatic impairment and severe renal impairment as drug clearance is decreased. An initial dose reduction to 6.25 mg, with a maximum daily dose of 12.5 mg, should be considered in these patients. The same decrease in dose should be implemented if a patient is concomitantly taking ketoconazole due to the P450 3A4 drug interaction.

Almotriptan, like other triptans, should be avoided in patients with ischemic heart disease, coronary artery vasospasm or other underlying cardiovascular disease, cerebrovascular syndromes, peripheral vascular disease, and uncontrolled hypertension.[6] All triptans are contraindicated in hemiplegic or basilar migraines.

They should not be taken within 24 hours of another triptan, ergotamine-containing, or ergotamine-similar medication. Careful monitoring should be exercised when a patient concomitantly uses selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors as reports of serotonin syndrome have been described.

Clinical Studies

There are three post hoc studies which initially evaluated the use of almotriptan for early versus late treatment of migraine headache.[8–10] The first was a post hoc analysis of an open label, long term trial investigating almotriptan for migraine attacks.[8] A total of 118 patients (n = 762 in the original study) who treated at least three attacks when the pain was mild and three attacks when the pain was moderate to severe were included in the post hoc analysis. Patients utilized almotriptan 12.5 mg for each headache treatment and were instructed to treat a migraine of any pain intensity in the original study. Efficacy was a secondary focus for this analysis. More patients who treated their attack when the pain was mild were pain free at one hour after almotriptan administration compared to those who waited to treat until the pain was moderate to severe (47% vs. 14%, $P < 0.001$). Also, patients who treated when the migraine pain was mild utilized less rescue medication (8% vs. 13%, $P < 0.01$) and experienced less headache recurrence (28% vs. 33%, $P = 0.01$) than those who waited to treat until the pain was of moderate to severe intensity. The incidence of adverse events was similar between the two groups (6% mild vs. 7% moderate to severe, no significant difference).

An additional post hoc analysis followed from another long term, open label, multicenter study assessing the use of almotriptan for migraine management.[9] A total of 582 patients who treated 10,645 attacks were assessed in the original study and this same patient population was utilized for this post hoc analysis. Patients utilized almotriptan 12.5 mg for each headache and were instructed to treat at the onset. Efficacy was the primary focus for this analysis. More patients who treated their attacks when the pain was mild were pain free at one hour (35.3% vs. 7.5%, $P < 0.001$) and two hours (76.9% vs. 43.9%, $P < 0.001$) after almotriptan administration compared to those who waited to treat when the pain was moderate to severe. In addition, patients who treated the headaches when the pain was mild experienced higher sustained pain free rates (66.6% vs. 36.6%, $P < 0.001$), experienced less headache recurrence (12.9% vs. 25.0%, $P < 0.001$) and utilized less rescue medications (9.4% vs. 17.2%, $P < 0.001$). Almotriptan was well tolerated in this study and the investigators did not report if there were differences in tolerability between the two groups.

The last post hoc analysis was conducted on a double blind, randomized, controlled trial comparing almotriptan to sumatriptan and placebo for migraine headaches.[10] The original multi-country study involved 475 patients of which 253 were included in the post hoc analysis (inclusion criteria: headache treatment administered within one hour of pain onset). Patients utilized almotriptan 12.5 mg (n = 95), sumatriptan 100 mg (n = 115) or placebo (n = 53) when the pain from a migraine attack was of moderate to severe intensity in the original study. The post hoc analysis only included the almotriptan 12.5 mg arm since the 25 mg dose was "not approved for use." Efficacy was the primary focus for this analysis. The pain free rates one hour after medication administration was higher in both the almotriptan and sumatriptan groups compared to placebo (37.9% vs. 35.7% vs. 18.9%, $P = 0.016$ and $P = 0.028$ respectively versus placebo). There was no significant difference between almotriptan and sumatriptan in pain free rates at one hour. Sustained pain free rates were higher with almotriptan compared to placebo (34.7% vs. 17.0%, $P = 0.022$). There was no difference in sustained pain free rates when comparing sumatriptan to placebo or almotriptan to sumatriptan. When stratified by pain intensity (moderate vs. severe), a higher percentage of patients were pain free at two hours and experienced higher sustained pain free rates in the moderate pain intensity group compared to the severe pain intensity group for both almotriptan and sumatriptan (no statistical analysis was reported). Almotriptan was tolerated as well as the placebo per the authors (event rate for placebo not reported and statistical analysis not provided) and was significantly better tolerated than sumatriptan (overall adverse event rates: 8.7% vs. 22.2%, $P < 0.001$).

Safety

Historically, almotriptan has been well tolerated with a similar side effect profile to placebo and

has a favorable adverse effect profile compared to other triptans.[6,11] The tolerability is similar in these early design treatment trials to previous almotriptan trials.[11–15] Adverse event rates are similar to placebo[13,16] and there was no significant difference in overall adverse event rates reported in those who treated the migraine headache early compared to late.[12,15]

Only two of the four early treatment studies reported premature discontinuation rates.[12,13] (See Table 1) The first was a head to head comparison of early to standard treatment with almotriptan. The early group had 4.2% withdraw while the standard treatment group had 3.3% withdraw due to intolerable adverse effects.[12] The second trial was a placebo controlled trial with identical discontinuation rates between almotriptan and placebo (0.6%). The most common adverse effects reported in these two early intervention trials were nausea, vomiting and somnolence.[12,13]

Only two studies reported serious adverse events.[12,13] The first reported three patients experiencing serious adverse events.[12] One patient who did not take a dose of study drug died from a myocardial infarction while enrolled. The other two patients were diagnosed with breast cancer and a right cerebellopontine angle tumor/aseptic meningitis, respectively. Both of these were determined to be unrelated to study drug use.[12] The second study reported two patients experiencing three serious adverse events (perforated appendix, peritoneal infection and pneumonia). All of these were considered unrelated to almotriptan or placebo treatment.[13]

Chest pain, chest tightness, and other cardiac related adverse events were only detailed in two of the four studies.[12,13] The incidence of chest pain (0.4%) and chest tightness (0.1%) were low in a study assessing early versus late treatment.[12] There were no cardiac related adverse events reported in a placebo controlled study with early almotriptan.[13]

Efficacy

The AIMS trial was a multicenter, open label, cluster randomized trial conducted in 2,443 patients treating two sequential migraine headaches.[12] The authors only reported results regarding treatment of the first headache (n = 1,450) in this publication. Patients were 18 to 65 years of age and had migraines with or without aura of at least moderate intensity for at least 1 year. They had to average 1 to 6 migraines per month over 3 months to be included in the trial. Patients utilized almotriptan 12.5 mg for headache treatment and were advised to either take it at earliest onset of headache pain, within 1 hour (early treatment group[ET]) or wait and treat when the headache pain was of moderate to severe intensity (standard treatment group[ST]). The primary focus for this study was efficacy (see Table 2 for specific primary and

Table 1. Tolerability/safety of almotriptan.

	Freitag, et al[12]	Mathew, et al[13,14]	Goadsby, Zachin, et al[16,17]	Lanteri–Minet[15]
Overall AE's %	11.9% ET & 10.7% ST	23.0% Almo & 23.7% Pl Deemed treatment related: 8.0% Almo vs. 4.0% Pl	4.9% Almo mild 4% Almo moderate/severe 4.7% Pl mild 4.0% Pl moderate/severe	65 (5.5%) total treatment-emergent adverse events reported in study NSD between ET and NET group
Specific AE's				
Nausea	2.1%	1.7% Pl & 1.1% Almo	NR	NR
Dizziness	0.9%	NR	NR	1 case
Vomiting	0.8%	0.6% Pl & 1.1% Almo	NR	NR
Somnolence	0.6%	2.3% Pl & 1.1% Almo	NR	NR
Palpitations	0.5%	NR	NR	NR
Chest pain	0.4%	NR	NR	NR
Chest tightness	0.1%	NR	NR	NR
Tremor	NR	NR	NR	1 case
Withdrawals due to AE's	4.2% ET & 3.3% ST	0.6% Almo & 0.6% Pl	None	None

Abbreviations: AE's, adverse effects; Almo, almotriptan; Pl, placebo; NR, not reported; NSD, no significant difference; ET, early treatment; NET, non-early treatment; ST, standard treatment.

Table 2. Efficacy of early use of almotriptan.

	Freitag, et al (AIMS)[12]	Mathew, et al (AEGIS)[13,14]	Goadsby, Zanachin, et al (AwM)[16,17]	Lanteri–Minet, et al (START)[15]
Design	Open label, cluster randomized, multicenter n = 1,450 (n = 757 ET & n = 693 ST) Duration: Treatment of 2 sequential migraine headaches	RCT, multicenter n = 378 (317 evaluated for efficacy [n = 162 almotriptan, n = 155 placebo] & 347 evaluated for safety [n = 174 almotriptan, n = 173 placebo]) Duration: 3 headaches	RCT, multicenter n = 491 (403 evaluable [n = 103 almo mild, n = 95 almo moderate/severe, n = 107 Pl mild, n = 98 Pl moderate/severe]) Duration: 1 headache	Open label, multicenter n = 501 (454 evaluable [first attack n = 42 ET & n = 410 NET, all attacks n = 138 ET & n = 1036 NET]) Duration: 3 headaches
Treatment	Two treatment groups, both received Almotriptan 12.5 mg ET-administer at earliest onset of headache pain (which also was to be within 1 hour of the onset of pain) ST-administer when headache pain was of moderate to severe intensity (if pain never reached moderate intensity patients were asked to wait 4 hours to treat)	Two treatment groups: Almotriptan 12.5 mg or placebo administered at earliest onset of headache of any intensity, within one hour of onset	Four treatment groups: Almotriptan 12.5 mg to utilize when pain was mild (within one hour of onset), placebo to utilize when pain was mild (within one hour of onset), almotriptan 12.5 mg to utilize when pain was moderate to severe or placebo to utilize when pain was moderate to severe	One treatment group: Almotriptan 12.5 mg within one hour of pain onset and when pain was mild Each headache was then stratified based on headache severity at time of treatment to analyze results: ET-treated when experienced mild pain, within one hour of headache onset NET-treated when experienced moderate/ severe pain, beyond one hour of headache onset

(*Continued*)

Table 2 (*Continued*)

	Freitag, et al (AIMS)[12]	Mathew, et al (AEGIS)[13,14]	Goadsby, Zanachin, et al (AwM)[16,17]	Lanteri-Minet, et al (START)[15]
Primary outcome	Total headache duration for the first headache (median): 3.18 hours ET vs. 5.53 hours ST, $P < 0.001$	2 hour pain free for the first headache: 37.0% almo vs. 23.9% Pl, $P = 0.010$	2 hour pain free (almo mild pain and early vs. almo moderate/severe pain): 49% Almo mild vs. 40% Almo moderate/severe, $P = 0.2154$ Of note, there were 19 subjects assigned to the Almo mild group that waited to treat the attack when pain was moderate to severe. When patients were reassigned based on this and the data reanalyzed, 54% in the Almo mild group were pain free at 2 hours compared to 37.5% in the Almo moderate/severe, $P = 0.02$. Both almo groups were significantly better than the placebo groups ($P = 0.0004$ and $P = 0.0002$).	2 hour pain free for the first headache: 61.9% ET vs. 35.37% NET, $P < 0.001$
Select secondary outcomes	2 hour pain free: 42.5% ET vs. 39.0% ST, $P = 0.210$ SPF: 17.3% ET vs. 15.3% ST, $P = 0.311$ Use of rescue medication: 35.5% ET vs. 36.9% ST, $P = 0.627$	Pain free (at 0.5, 1, 4 and 24 hours): All time points were statistically significantly better than placebo except for 0.5 hrs. Pain relief (at 0.5, 1, 2, 4 and 24 hours): All time points were statistically significantly better than placebo except for 0.5 hrs. Modified pain relief (at 0.5, 1,2, 4, and 24 hours): All time points were statistically significantly better than placebo except for 0.5 hrs. SPF: 24.7% Almo vs. 16.1% Pl, $P = 0.04$ Use of rescue medication: 0 to 4 hours: 27.3% Almo vs. 50.3% Pl, $P < 0.0001$ 0 to 24 hours: 39.5% Almo vs. 60.6% Pl, $P < 0.0001$ Functional disability at BL, 1,2,4 and 24 hours- BL: NSD ($P = 0.758$) for any functionality class 1 hr: NSD ($P = 0.986$) for any functionality class 2 hr: BL-N: 54.4% Almo vs. 38.1% Pl ($P = 0.007$), D: 32.5% Almo vs. 45.2% Pl ($P = 0.007$), BR: 13.1% Almo vs. 16.1% Pl ($P = 0.007$),	SPF: 46% Almo mild, 30% Almo moderate/severe, 16% Pl mild & 11% Pl moderate/severe Almo mild vs. Almo moderate/severe, $P = 0.024$ Both Almo mild and Almo moderate/severe vs. placebo, $P = 0.0018$ & $P < 0.0001$, respectively Use of rescue medication: NSD between the Almo mild and Almo moderate/severe treatment arms. Both Almo groups used significantly less rescue meds than the Pl groups ($P < 0.0001$). Headache recurrence within 24 hours: 6.0% Almo mild, 24% Almo moderate/severe, 37% Pl mild & 27% Pl moderate/severe. There was a significant difference between Almo mild and Almo moderate to severe ($P = 0.0124$). Headache recurrence between 24 and 48 hours: NSD across all four treatment arms. Total attack duration (median): 2.0 hours Almo mild vs. 5.0 hours Almo moderate/severe, $P = 0.0005$. Placebo durations not reported. Time lost to the attack: 0 hours Almo mild vs. 2 hours Almo moderate/severe, $P = 0.0015$. Both placebo groups were 2 hours, no statistical analysis reported. Allodynia subgroup analysis: Mild- 2 hour pain free: 53.9% Almo with allodynia vs. 52.5% Almo without allodynia (P = NS) SPF: 47.2% Almo with allodynia vs. 45.5% Almo without allodynia (P value not provided) Duration: 1.40 hours Almo with allodynia vs. 1.54 hours Almo without allodynia (P value not provided)	2 hour pain free across all attacks: 65.22% ET vs. 37.64% NET, $P < 0.001$ SPF: 59.42% ET vs. 32.82% NET, $P < 0.001$ SPF with no adverse events: 55.07% ET vs. 31.27% NET, $P < 0.001$ Relapse at 24 hours: NSD Use of rescue medications: 15% ET vs. 37% NET, $P = 0.003$ Median duration of migraine: 2 hour 10 minutes ET vs. 5 hours NET, $P < 0.001$ Mean time lost to attack: 51 minutes ET vs. 1 hour 46 minutes NET, $P < 0.001$

H/ER: none for Almo vs. 0.6% Pl	Moderate to Severe- 2 hour pain free: 31.4% Almo with allodynia vs. 44.3% Almo without allodynia ($P = 0.16$)	
4 hr: BL- N: 74.5% Almo vs. 54.3% Pl ($P < 0.001$), D: 20.1% Almo vs. 29.3% Pl ($P < 0.001$), BR: 4.7% Almo vs. 15.7% Pl ($P < 0.001$),	2 hour pain relief: 53% Almo with allodynia vs. 72% Almo without allodynia, $P = 0.036$ SPF: data not reported Duration: 3.17 hours Almo with allodynia vs. 1.87 hours Almo without allodynia (*P* value not provided)	
H/ER: 0.7% Almo vs. 0.7% Pl	Rescue Medication Use: 45% Almo with allodynia vs. 23% Almo without allodynia, $P = 0.05$	
24 hr: NSD ($P = 0.954$) for any functionality class	Rescue Medication Use: 15% Almo early with allodynia vs. 45% Almo moderate to severe with allodynia ($P = 0.0195$) Almo early without allodynia 29% vs. Almo moderate to severe without allodynia 23% ($P = 0.47$)	

Abbreviations: ET, early treatment; ST, standard treatment; SPF, sustained pain free (2 to 24 hours after treatment with no rescue medication use); Almo, almotriptan; Pl, placebo; PF, pain free; NSD, no significant difference; NS, not significant; NET, non-early treatment; BL, baseline; N, normal function; D, disturbed function; BR, bed rest; H/ER, hospitalization/emergency room visit.

secondary outcomes). The median time to treatment in the ET group was significantly shorter in the ST group (10 minutes vs. 90 minutes, $P < 0.001$). Patients who were treated early had significantly shorter median headache durations than those who waited to treat (3.18 hours vs. 5.53 hours, $P < 0.001$). There were no differences in two hour pain free rates, sustained pain free rates or utilization of rescue medications between the two groups (see Table 2 for specifics). Subgroup analysis was performed on headache intensity and time to treatments. There were 105 patients removed from the subgroup analyses as they were assigned to the ET group but did not treat early, providing 652 in ET group and 693 patients in the ST group for evaluation. Median headache duration was shorter when pain was mild or moderate at time of treatment compared to severe (ET $\leq$ 1 hour- mild 2.63 hours, moderate 2.75 hours, severe 24.00 hours, $P < 0.001$ severe vs. mild and moderate; ST $\leq$1 hour- moderate 2.17 hours, severe 10.5 hours, $P < 0.001$; ST $\geq$ 1 hour- moderate 7.00 hours, severe 24.00 hours, $P = 0.016$). In addition, patients who treated their migraine when the headache was mild to moderate had higher 2 hour pain free rates, higher sustained pain free rates and utilized less rescue medications than those who waited till the headache was severe to treat.

The AEGIS trial was a multicenter, double blind, randomized controlled trial which enrolled 378 patients treating three migraine headaches.[13] Patients were 18 to 65 years of age and had migraines with or without aura of at least moderate intensity for at least 1 year. They had to have 2 to 6 migraines per month for the last three months to be included in the trial. Only 317 patients were evaluable for efficacy, the primary focus for this trial (see Table 2 for specific primary and secondary outcomes). Patients utilized almotriptan 12.5 mg or placebo at first sign of headache of any intensity, within one hour of onset. Significantly more patients were pain free at 2 hours with almotriptan compared placebo (37.0% vs. 23.9%, $P = 0.010$). Also more patients were pain free at other time intervals (1 to 24 hours), experienced pain relief at other time intervals (1 to 24 hours), and achieved sustained pain relief up to 24 hours when treated with almotriptan compared to placebo (see Table 2 for details). However, there were no significant differences between groups at 30 minutes after dose administration. In addition, patients treated with almotriptan utilized

significantly less rescue medications at any time point than those taking placebo. Other results from AEGIS were published separately[14] regarding functional disability. Patient functionality was categorized as either normal, disturbed (normal activities disturbed but can continue), bed rest required, or hospitalization/emergency room (ER) visit required. Functional disability significantly improved 2 hours post treatment and 4 hours post treatment with almotriptan (see Table 2 for details). There was no difference seen in functional disability at 1 hour and 24 hours between almotriptan and placebo.

The AwM study was a multicenter, double blind, randomized controlled trial which enrolled 491 migraine patients to treat one headache of which 403 patients were evaluable.[16] Patients were 18 to 65 years of age and had migraines with or without aura of at least moderate intensity for at least 1 year. They had to have 2 to 6 migraines per month for the last three months to be included in the trial. The primary focus was efficacy (see Table 2 for specific primary and secondary outcomes). Patients were assigned to one of four treatment groups: almotriptan 12.5 mg to utilize when pain was mild (within one hour of onset), placebo to utilize when pain was mild (within one hour of onset), almotriptan 12.5 mg to utilize when pain was moderate to severe, or placebo to utilize when pain was moderate to severe. In the initial analysis, there was no significant difference in 2 hour pain free rates between the almotriptan mild and the almotriptan moderate to severe groups (49% vs. 40%, $P = 0.2154$). However, the investigators realized after unblinding that 21 patients in the almotriptan assigned groups had not treated according to treatment assignment (19 in the mild group waited to treat until pain was moderate to severe and 2 in the moderate to severe group treated when pain was mild). Upon "reassignment" to treatment groups based on treatment time and severity of pain, there was a significant difference in those who were pain free at 2 hours between the almotriptan groups (54% mild vs. 37.5% moderate to severe, $P = 0.02$). Patients who treated early with almotriptan, when the pain was mild, had higher sustained pain free rates, shorter attack durations and experienced less headache recurrence 24 hours after onset than those who waited to treat until the pain was moderate to severe (see Table 2 for complete results). There was no significant difference in the two almotriptan groups in use of rescue medication. Both almotriptan groups were significantly better than placebo for most outcomes (see Table 2 for complete results).

Similar to AEGIS, the AwM trial also had a separate publication addressing secondary outcomes focused on the associated allodynia and efficacy with almotripran.[17] Thirty-nine percent of the patients experienced allodynia in this study, 33% were in the early mild group and 45% were in the moderate to severe group. The presence or absence of allodynia in the early mild group did not impact 2 hour pain free rates, sustained pain free rates or duration of migraine (see Table 2 for complete results). The presence or absence of allodynia did not significantly impact 2 hour pain free rates in the moderate to severe group either. However, in patients with allodynia the 2 hour pain relief rate was significantly less and there was an increase use of rescue medications in the moderate to severe group compared to the early mild group (see Table 2 for complete results). Thus, emphasizing early treatment is beneficial. Based on the results, the author's determined that allodynia did not predict a poor response to almotripran therapy, but rather baseline headache pain severity was a predictor for response to therapy.

The START trial was a multicenter, open label conducted in 501 patients, with 454 who were evaluable.[15] Patients were 18 to 65 years of age and had migraines with or without aura of at least moderate intensity for at least 1 year. They had to have 2 to 6 migraines per month for the last three months to be included in the trial. Patients were instructed to utilize almotriptan 12.5 mg within one hour of pain onset and when pain was mild for three headaches. Headaches were then stratified to one of two treatment groups based on headache severity at time of treatment: early treatment (within 1 hour of pain and mild headache severity) or non-early treatment (beyond 1 hour of pain and moderate to severe headache severity). Efficacy was the primary focus for this study (see Table 2 for specific primary and secondary objectives). Significantly more patients who treated their mild headache early were pain free at two hours for the first headache (61.9% vs. 35.37%, $P < 0.001$) compared to those who waited until the pain was moderate to severe. Patients who treated with almotriptan early, when the pain was mild, had higher 2 hour pain

free rates across all attacks, higher sustained pain free rates, shorter attack durations and utilized less rescue medications after onset than those who waited to treat until the pain was moderate to severe (see Table 2 for complete results). There was no significant difference in headache recurrence within 24 hours after treatment between the two groups.

Place in Therapy

Almotriptan is considered as a first line treatment option for acute migraines in adults and adolescents. Other triptans (sumatriptan, rizatriptan, zolmitriptan, eletriptan, frovatriptan) have been evaluated for use of early treatment of migraines, but lack of clear definitions of 'mild' or 'early' and weaknesses in study design and methods hinder their clinical application to practice.[8,10] Not all patients have the opportunity to treat 'early' in the course of a migraine as they may wake with pain already at a level of moderate or severe or the patient's migraine may quickly escalate from mild to moderate or severe. One migraine study determined only 50% of all migraines attacks have the opportunity to be treated early and when the pain is mild.[18] However, if early treatment is an option and practiced, the patient may be able to reduce pain, prevent recurrence, and continue with daily activities.

Patient Preference

None of the studies in the early trials of almotriptan inquired about patient preference. Patient preference of the triptan class typically depends on formulation and the pharmacokinetic profile of the individual medication. Numerous formulations ranging from oral tablets, rapid dissolving tablets, subcutaneous injections and nasal sprays are available. Each triptan in the class has different pharmacokinetic characteristics which allows for variation in onset and duration of action. Almotriptan is only available in an oral tablet and of the class, has a quicker onset and longer duration of action. Certain patients may prefer non-oral dosage forms due to severe nausea and vomiting associated with a migraine. Patients however, may prefer almotriptan due to the pharmacokinetic profile and clinical efficacy they receive from the medication. Migraine patients in general seek treatment options that provide a fast onset and complete pain and symptom relief of the migraine. Medications that are tolerable, lack adverse effects and prevent the migraine from returning are ideal. Almotriptan has shown these qualities in clinical studies.

Conclusions

Migraine headaches are a common chronic, disabling disease state. Patients seek acute treatment options that result in a quick onset of pain and symptom relief, prevent reoccurrence, and enable the patient to continue with daily activities. Almotriptan has demonstrated these characteristics when administered within one hour of onset of headache and while the pain is described as mild. Tolerability has been similar to placebo and adverse effects were minimal in clinical trials. Almotriptan is a viable option for early treatment of migraines in patients.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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