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A Review of Recent Clinical Experience with Almotriptan

Hans-Christoph Diener

Department of Neurology, University of Duisburg-Essen, D45122 Essen, Federal Republic of Germany

Abstract

The purpose of this paper is to review six recently completed trials (three double-blind, three open-label) providing valuable data on efficacy and tolerability of almotriptan in 'real world' settings.

In a randomized double-blind trial, almotriptan 12.5 mg and zolmitriptan 2.5 mg achieved similar efficacy rates whereas almotriptan was associated with a lower rate of triptan-associated adverse events (AE). In another randomized double-blind trial, almotriptan patients achieved significantly higher 2-h pain-free, 2-h pain-relief and sustained pain-free rates than those receiving ergotamine plus caffeine. A third double-blind trial, enrolling patients with a history of poor response to sumatriptan (confirmed in a prerandomization attack), showed that patients receiving almotriptan had significantly higher 2-h pain-free, 2-h pain-relief and sustained pain-free rates compared with those receiving placebo.

An open-label trial found similar rates of preference for almotriptan and rizatriptan 10 mg; similar rates were also seen for 2-h pain free, 2-h pain relief and sustained pain free. The German Migraine Register (open-label) found triptans to be associated with greater treatment satisfaction than non-specific agents; almotriptan and sumatriptan were linked to the highest levels of patient satisfaction. Another open-label satisfaction study showed that in comparison with previous therapies, almotriptan was associated with higher rates of pain relief, tolerability, resumption of normal activities, and the use of only one dose.

In summary, the high levels of efficacy and tolerability reported for almotriptan 12.5 mg in earlier placebo-controlled clinical trials can be reproduced in 'real-world' clinical settings, and are consistent with previous trials showing almotriptan to have the ideal profile for an acute migraine treatment, that is, a balance between high efficacy and low AEs.

1. Introduction

The efficacy and placebo-like tolerability of oral almotriptan have been demonstrated in several randomized, double-blind, controlled clinical trials.[1–7] More recently, a meta-analysis of 53 trials of oral triptans identified almotriptan 12.5 mg as being one of three triptans (the others being rizatriptan 10 mg and eletriptan 80 mg) most likely to be associated with treatment success; this

conclusion was based on comparisons of efficacy, consistency of effect, and tolerability with sumatriptan 100 mg.[8] The meta-analysis also corroborated the placebo-like tolerability profile of almotriptan 12.5 mg.[8]

Further support for the use of almotriptan comes from several recent postmarketing trials that provide useful data on the efficacy and tolerability of almotriptan in 'real world' settings. Postmarketing studies often include greater numbers of patients and a more diverse patient population, allowing for the identification of differences in drug efficacy, tolerability and safety in migraineurs with different co-morbidities, immune systems, drug metabolism and drug–drug interactions.[9] In addition, postmarketing trials often measure endpoints relevant to patient satisfaction and preference that were not necessary for marketing approval. This article will describe the findings of several new postmarketing studies of almotriptan 12.5 mg, including direct comparative data for almotriptan versus other triptans and versus ergotamine plus caffeine, the efficacy of almotriptan in patients with poor response to sumatriptan, and data on patient satisfaction with almotriptan therapy.

2. New Randomized, Double-blind Clinical Trials

2.1. Almotriptan versus Zolmitriptan Trial

The Almotriptan versus Zolmitriptan Trial was a double-blind, parallel-group study conducted in 119 centres in nine European countries (Belgium, Finland, France, Germany, Italy, Portugal, Spain, Sweden, and the United Kingdom; table I).[10] Patients ($N = 1062$) were randomly assigned to almotriptan 12.5 mg or zolmitriptan 2.5 mg (both encapsulated; no placebo arm), and were instructed to treat a single migraine attack when headache pain was moderate to severe. The primary endpoint was sustained pain free plus no adverse events (AE). Secondary efficacy assessments included sustained pain free, the proportion of patients with pain relief and those pain free at 30, 60, 90 and 120 min after treatment, functional level at 2 h and patients' satisfaction with therapy. Tolerability outcomes included the proportion of patients with treatment-emergent AE, triptan-associated AE and triptan-associated central nervous system (CNS) AE.

Patients enrolled in the trial were adult migraineurs receiving treatment from neurologists. The included patients had a migraine history of at least 12 months diagnosis according to International Headache Society (IHS) criteria, had two to six migraine attacks per month during the 2 months before enrollment, and did not experience hemiplegic or basilar migraine or tension-type headache on more than 4 days/month. Those with previous or current triptan treatment, including usage of the study drugs, were permitted to enroll. A history of triptan usage was available for approximately half of the patients; 42% were triptan naive.

Almotriptan 12.5 mg and zolmitriptan 2.5 mg were associated with similar efficacy because sustained pain free plus no AE rates for the almotriptan (30.5%) and zolmitriptan groups (32.0%) were not significantly different. The two triptans also did not differ in any of the secondary efficacy endpoints measured (2-h pain free: 45.6 versus 48.5%; 2-h pain relief: 67.7 versus 71.6%; sustained pain free: 35.9 versus 38.1%; use of rescue medication within 24 h: 19.1 versus 20.2%; recurrence within 24 h: 22.5 versus 21.0%, almotriptan versus zolmitriptan, respectively). In addition, the almotriptan and zolmitriptan groups did not differ significantly with respect to the proportion of patients with pain relief and those pain free at 30, 60, 90, and 120 min after treatment. The ability to function was similar among the two treatment groups: at 2 h, approximately half of the patients in each group were not impaired, and approximately a quarter had minimal impairment. More than half of the patients in each group described their satisfaction with treatment as 'excellent' or 'good'.

The proportion of patients reporting treatment-emergent AE in the almotriptan and zolmitriptan groups was not significantly different (19.2 versus

Table I. Almotripan postmarketing randomized, double-blind, controlled trials

	Almotriptan vs zolmitriptan[10]	Almotriptan vs ergotamine[11]	Sumatriptan non-responders[12]
Countries	9 European countries[a]	Spain	Germany
No. of patients	1062 enrolled 1061 intent-to-treat	229 randomized 182 evaluated for efficacy	328 enrolled 221 randomized
Attacks treated	1 attack, moderate to severe	2 attacks	1 attack[b]
Agents	Almotriptan 12.5 mg Zolmitriptan 2.5 mg	Almotriptan 12.5 mg Ergotamine 2 mg + caffeine 200 mg	Almotriptan 12.5 mg Placebo
Other protocol details	Previous/current triptan users not excluded Both drugs encapsulated	Crossover design Both drugs encapsulated	Enrolled patients with history of poor response to sumatriptan (≥ 2 attacks) Open-label run-in phase with single attack treated with sumatriptan 50 mg → non-responders randomized
Assessments	Sustained pain free plus no AE Sustained pain free 2-h PF 2-h PR AE	2-h PF 2-h PR Sustained pain free Rescue medication use AE	2-h PF 2-h PR Sustained pain free AE
Conclusions	Almotriptan and zolmitriptan were associated with similar efficacy and overall tolerability; almotriptan was associated with a significantly lower rate of triptan-associated AE	Almotriptan was associated with a significantly higher rate of 2-h PF, 2-h PR, sustained pain free, sustained pain free plus no AE and relief from migraine-associated symptoms compared with ergotamine plus caffeine; almotriptan was well tolerated with a low incidence of AE	Almotriptan was associated with a significantly higher rate of 2-h PF, 2-h PR and sustained pain free compared with placebo in patients who were previously poor responders to sumatriptan

AE = Adverse events; **2-h PF** = pain-free at 2 h; **2-h PR** = pain-relief at 2 h.
[a] Belgium, Finland, France, Germany, Italy, Portugal, Spain, Sweden, and the United Kingdom.
[b] During the double-blind phase of the trial.

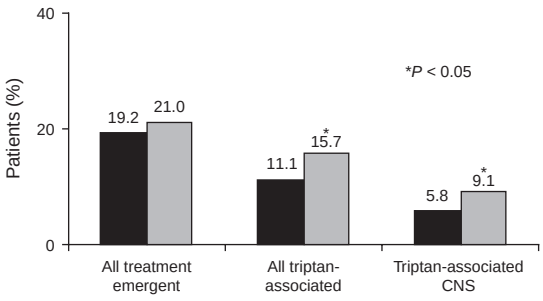

Fig. 1. Adverse events after treatment with almotriptan 12.5 mg and zolmitriptan 2.5 mg from a randomized, double-blind, multicentre European trial.[10] **CNS** = Central nervous system. $^{*}P < 0.05$ zolmitriptan versus almotriptan by chi-square analysis. Analyses of triptan-associated adverse events were *post hoc*. ■ = Almotriptan; □ = zolmitriptan.

21.0%, respectively; figure 1). However, a significantly smaller proportion of patients receiving almotriptan (11.1%) reported triptan-associated AE compared with patients receiving zolmitriptan (15.7%, $P < 0.05$). Likewise, a significantly lower proportion of the almotriptan-treated patients reported triptan-associated CNS AE compared with zolmitriptan-treated patients (5.8 versus 9.1%, $P < 0.05$).

In summary, the Almotriptan versus Zolmitriptan Trial was a large, rigorously conducted randomized trial in which difficult-to-achieve efficacy endpoints such as sustained pain free plus no AE and sustained pain free were measured. Almotriptan and zolmitriptan were associated with similarly

high levels of efficacy, restoration of function, and satisfaction with treatment. With its lower rate of triptan-associated AE and triptan-associated CNS AE, almotriptan was found to have better tolerability than zolmitriptan.

2.2. Almotriptan versus Ergotamine Trial

The Almotriptan versus Ergotamine Trial was a randomized, double-blind, two-attack, crossover, multicentre study conducted in 24 sites in Spain (table I).[11] Patients were randomly assigned one-to-one to almotriptan 12.5 mg or ergotamine 2 mg plus caffeine 200 mg (both almotriptan and ergotamine plus caffeine were encapsulated; no placebo arm). A total of 229 patients were randomly assigned, and 182 were evaluated for efficacy. Efficacy assessments included 2-h pain free, 2-h pain relief, sustained pain free and the use of rescue medication. AE were recorded. This trial enrolled adult patients with at least a one-year history of migraine (diagnosis according to IHS criteria) who had experienced one to six migraines per month during the year before the study.

Almotriptan was associated with greater efficacy than ergotamine plus caffeine as shown by the significantly higher rates for 2-h pain free (20.9 versus 13.7%, $P < 0.05$), 2-h pain relief (57.7 versus 44.5%, $P < 0.01$) and sustained pain free (20.3 versus 11.5%, $P < 0.0.5$; figure 2). In addition, rescue medication was used by 38.5% of almotriptan-treated patients compared with 48.3% of ergotamine plus caffeine-treated patients ($P < 0.05$). Almotriptan was also associated with greater relief of migraine-associated symptoms including nausea, vomiting, and phonophobia. Treatment with almotriptan was associated with a lower rate of AE compared with ergotamine plus caffeine (7.0 versus 11.8%, $P = 0.06$), although this difference did not reach significance.

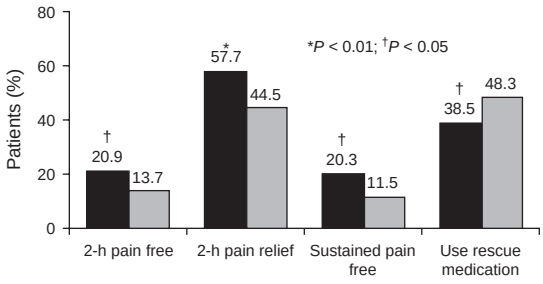

Fig. 2. Efficacy of treatment with almotriptan 12.5 mg versus ergotamine 2 mg plus caffeine 200 mg (both encapsulated) from a randomized, double-blind, two-attack, crossover, multicentre trial conducted in Spain.[11] ■ = Almotriptan; □ = ergotamine plus caffeine.

In summary, almotriptan 12.5 mg was found to have significantly greater efficacy and better tolerability than ergotamine 2 mg plus caffeine 200 mg for the acute treatment of migraine.

2.3. Sumatriptan Non-responder Trial

The Sumatriptan Non-responder Trial was a randomized, double-blind, placebo-controlled study conducted in 60 outpatient centres in Germany that assessed the efficacy of almotriptan 12.5 mg in patients with inadequate response to sumatriptan (table I).[12] A total of 328 enrolled patients who had experienced unsatisfactory responses to sumatriptan on at least two previous occasions were evaluated prospectively for their response to open-label oral sumatriptan 50 mg in a single migraine attack. Patients not responding to sumatriptan (defined as having moderate or severe headache pain 2 h after treatment) were eligible to continue in the study; these patients were randomly assigned to receive two doses of almotriptan 12.5 mg or placebo for treatment of their next migraine attack. The first dose was to be taken as soon as possible after the onset of moderate to severe migraine headache pain; the second dose could be taken within 2–24 h if headache pain reoccurred during this time. Rescue medication was permitted if moderate to severe headache pain persisted 2 h after taking the study medication. Efficacy assessments included 2-h pain relief, 2-h pain free and sustained pain free. AE were recorded.

The study enrolled adult patients who experienced migraine with or without aura (IHS criteria), who had at least one moderate/severe attack per

month in the 2 months preceding the trial, and who had a history of poor response to oral sumatriptan (two or more attacks). Patients were excluded if they had complex forms of migraine, tension-type headache on 15 or more days per month, or were unable to distinguish migraine from non-migraine types of headache.

Headache pain was severe for 70% of the patients at the time of treatment with the study drug. Almotriptan was associated with significantly greater efficacy compared with placebo as shown by rates for 2-h pain relief (47.5 versus 23.2%, $P < 0.001$), 2-h pain free (33.3 versus 14.1%, $P < 0.005$) and sustained pain free (20.9 versus 9%, $P < 0.05$; figure 3a). A total of 16.2% of patients reported AE while receiving sumatriptan during the open-label phase of the trial; the AE rates associated with almotriptan and placebo, 7.1 and 5.1%, respectively, during the randomized phase were not significantly different (figure 3b).

These findings indicate that a poor response to one triptan does not predict a poor response to other agents in that class. Patients with previous inadequate responses to sumatriptan 50 mg responded well to almotriptan 12.5 mg as shown by 2-h pain relief, 2-h pain-free and sustained pain-free rates superior to placebo, despite a high rate of severe headache pain at baseline. The lack of statistical difference in AE rates between almotriptan and placebo indicates a placebo-like tolerability with almotriptan.

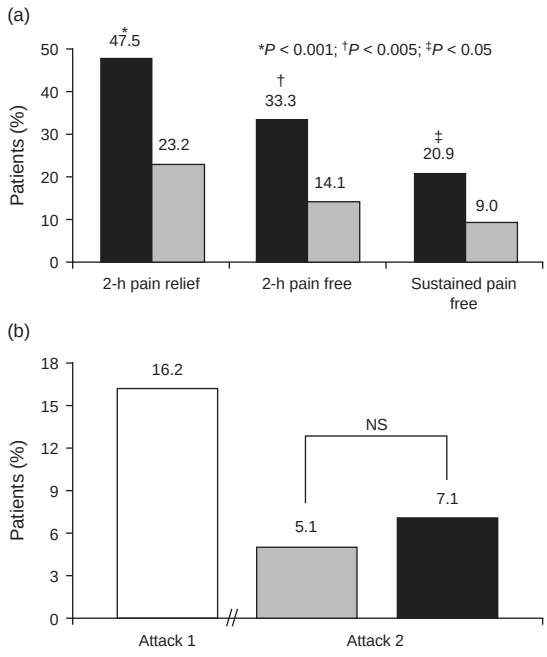

Fig. 3. Sumatriptan Non-responder Trial results. (a) Efficacy of almotriptan 12.5 mg and placebo during attack 2 of a two-attack trial for patients with a history of poor response to sumatriptan and demonstrated non-response to sumatriptan 50 mg during attack 1 of the trial. □ = Placebo; ■ = almotriptan 12.5 mg. (b) Proportion of patients reporting adverse events with sumatriptan 50 mg during attack 1 and with almotriptan 12.5 mg and placebo during attack 2.[12] □ = Sumatriptan 50 mg; ▒ = placebo; ■ = almotriptan 12.5 mg.

3. New Open-label Trials

3.1. Open-label Preference Trial in Migraine: Almotriptan versus Rizatriptan

The Open-label Preference Trial in Migraine: Almotriptan versus Rizatriptan (OPTIMAR) study was an open-label, two-attack, crossover study conducted in 58 centers in Germany, Italy, and Spain (table II).[13] Enrolled patients ($N = 372$) were instructed to treat two migraines within 84 days with study medication and were randomly assigned to a treatment sequence. Half of the patient population was to treat the first migraine with almotriptan 12.5 mg and the second migraine with rizatriptan 10 mg; the treatment sequence was reversed for the other half of the patient population. Efficacy assessments included patient preference, 2-h pain relief, 2-h pain free and sustained pain free. Tolerability assessments included treatment-emergent AE and triptan-associated AE.

Enrolled patients were adults with a history of migraine (diagnosed according to IHS criteria) of at least 6 months with onset before the age of 50 years. These patients had to have experienced two to six migraines per month during the 2 months preceding the study. The trial was restricted to triptan-naive patients.

The proportion of patients preferring almotriptan was not significantly different from that of patients preferring rizatriptan (54.5% for almotriptan versus

Table II. Almotripan postmarketing open-label clinical trials

	OPTIMAR[13]	German Migraine Register[14]	MISTRAL[15]
Countries	Germany Italy Spain	Germany	France
No. of patients	372 enrolled 327 intent-to-treat	937 patients	434 enrolled 342 evaluable
Attacks treated	2 attacks per patient	Multiple attacks during 90-day period after receiving a new prescription	Up to 3 attacks per patient (929 total attacks)
Agents	Almotriptan 12.5 mg vs rizatriptan 10 mg	Various non-specific and specific acute oral antimigraine agents	Almotriptan 12.5 mg
Other protocol details	Crossover design	Patients given new migraine treatments recruited	Patients dissatisfied with previous therapy as shown by ≥ 1 negative answer in the ANAES questionnaire
	Triptan-naive patients	Data collected by trained telephone call centre staff	
Assessments	Preference 2-h PR	Satisfaction	ANAES questions: (1) Do you experience significant relief within 2 h after taking your medication?
	2-h PF		(2) Do you tolerate your medication well?
	Sustained pain free		(3) Can you rapidly resume normal occupational, social, and family activities?
	AE		(4) Do you take only one dose of medication?
Conclusions	More patients preferred almotriptan over rizatriptan; almotriptan and rizatriptan were associated with similar rates of 2-h PF, 2-h PR and sustained pain free	Triptans were associated with greater satisfaction compared with non-specific agents; of the triptans, sumatriptan and almotriptan were linked to the greatest patient satisfaction	Almotriptan was effective, well tolerated and associated with a high rate of treatment satisfaction in migraineurs whose previous treatments were inadequate according to the ANAES recommendations

AE = Adverse events; **ANAES** = National Agency for Accreditation and Evaluation in Health; **2-h PF** = pain-free at 2 h; **2-h PR** = pain-relief at 2 h; **MISTRAL** = Migraine – Satisfaction with Treatment: Reality with Almogran study; **OPTIMAR** = Open-label Preference Trial in Migraine: Almotriptan versus Rizatriptan study.

45.5% for rizatriptan in the analysis of two attacks), and patients' preferences for almotriptan and rizatriptan were largely based on efficacy. Both almotriptan 12.5 mg and rizatriptan proved to be efficacious. Almotriptan and rizatriptan were associated with similar rates for 2-h pain relief (76.7 versus 78.7%, NS), 2-h pain free (57.9 versus 59.6%, NS) and sustained pain free (45.9 versus 47.2%, NS) for the two attacks; comparable results were observed in the analysis of the first attack only.

Almotriptan and rizatriptan were both well tolerated. Analysis of data from the two attacks showed that almotriptan was associated with lower rates of treatment-emergent AE (16.9% for almotriptan versus 18.5% for rizatriptan) and triptan-associated AE (8.4% for almotriptan versus 12.3% for rizatriptan). The rate of triptan-associated AE during treatment of the first attack only, when patients were triptan naive, was significantly lower for almotriptan (8.5%) compared with that for rizatriptan (18%, $P < 0.05$).

In summary, almotriptan and rizatriptan were similarly efficacious. Almotriptan was associated with better tolerability.

3.2. German Migraine Register Trial

The German Migraine Register Trial was an open-label study conducted in 151 outpatient clinics in Germany designed to assess satisfaction with recommended medical therapies for migraine (table II).[14] Patients were recruited to the Register when they were given a new prescription for migraine, and the patients were interviewed by a trained call centre staff member 90 days after receiving their new prescription. The German Migraine Register enrolled adult patients with a history of migraine with or without aura for at least one year who experienced one or more migraine attacks per month.

Results showed triptans to be associated with greater satisfaction compared with non-specific agents such as opioids, aspirin, and paracetamol. Of the triptans, sumatriptan and almotriptan were linked to the greatest patient satisfaction in the study.

3.3. Migraine – Satisfaction with Treatment: Reality with Almogran

The Migraine – Satisfaction with Treatment: Reality with Almogran (MISTRAL) study was an open-label, multicentre study conducted in France that assessed the efficacy, tolerability, and satisfaction with almotriptan 12.5 mg therapy in migraineurs who were not completely satisfied with their previous acute migraine treatment (table II).[15] Patients treated three successive migraine attacks with almotriptan 12.5 mg; study medication could be taken at the onset of headache pain of any intensity. Assessments, performed by neurologists, included the questionnaire developed by the National Agency for Accreditation and Evaluation in Health (ANAES) in collaboration with the French Headache Society (Société Française d'Etudes des Migraines et Céphalées; SFEMC),[16] patients' overall satisfaction with treatment, and AE.

Patients were recruited by 154 neurologists, who could enroll one to four migraineurs each. Enrollment was limited to adult patients with a diagnosis of migraine according to IHS criteria who experienced at least three migraine attacks per month in the 3 months preceding the study and whose previous experience with acute migraine therapy was unsatisfactory. The requirement of dissatisfaction with the previous therapy was met if the patient responded 'No' to at least one of the ANAES questions: (1) Do you experience significant relief within 2 h after taking your medication? (2) Do you tolerate your medication well? (3) Can you rapidly resume normal occupational, social, and family activities? and (4) Do you take only one dose of medication? Patients were excluded if they had their first migraine attack after the age of 50 years, had more than six migraines per month or headache for more than 15 days per month, analgesic use more than 10 days per month, prolonged aura or basilar or hemiplegic migraine.

Data for 929 attacks were obtained from 434 patients (342 evaluable). Responses to the ANAES questionnaire given at the end of the study compared with those given upon inclusion showed that in comparison with patients' previous therapies, almotriptan was associated with a greater proportion of patients experiencing significant relief at 2 h (69.3% with almotriptan versus 26.6% for the previous therapies), a greater proportion of patients tolerating treatment well (91.2 versus 76.0%), a greater proportion of patients returning to normal activities quickly (70.5 versus 24.9%), and a larger proportion of patients taking only one dose of medication (59.4 versus 28.1%; figure 4). At the conclusion of the trial, after almotriptan treatment, 73.1% of the patients answered 'Yes' to at least one additional ANAES question compared with their responses at the onset of the study, and 40.9% answered 'Yes' to all four ANAES questions. A total of 69% of the patients were either very satisfied or satisfied overall with almotriptan therapy. Of the patients who had tolerated other triptans poorly, 55.4% experienced no AE with almotriptan.

In summary, the MISTRAL study demonstrated that almotriptan 12.5 mg was effective, well tolerated and associated with a high rate of treatment satisfaction in migraineurs whose previous treatments were inadequate according to the ANAES recommendations.

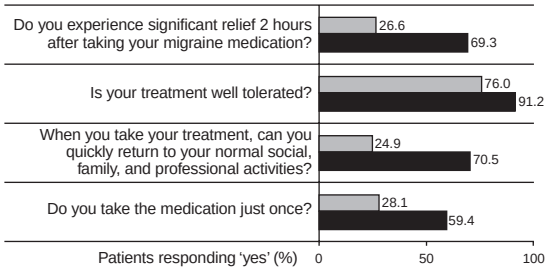

Fig. 4. Proportion of patients responding 'Yes' to questions from the National Agency for Accreditation and Evaluation in Health questionnaire in the Migraine Satisfaction with Treatment: Reality with Almogran trial on inclusion and at the end of the study after treatment of up to three successive migraine attacks with almotriptan 12.5 mg.[15] □ = On inclusion; ■ = End of study (after almotriptan treatment).

4. Discussion

Recent clinical trials with almotriptan 12.5 mg corroborate that the high levels of efficacy and tolerability reported in earlier placebo-controlled clinical trials can be reproduced in 'real world' clinical settings in a broad population of individuals with migraine. Direct comparator trials report efficacy rates for almotriptan equivalent to those for zolmitriptan and rizatriptan and superior to those of ergotamine plus caffeine. Almotriptan was also found to be efficacious in patients who were poor responders to sumatripan, providing greater hope for migraine sufferers and leading investigators to recommend switching triptans in patients who did not achieve a satisfactory result with a previous tripan.[17,18]

The recent clinical trials described here found high levels of patient satisfaction with almotriptan in both triptan-naive patients and in patients dissatisfied with their previous acute migraine therapy. One of the reasons for patient satisfaction with almotripan is its association with a low rate of AE, especially triptan-associated AE. Almotriptan's excellent tolerability could be used as a factor in encouraging patients to take their acute migraine therapy earlier in the progression of their headache. Studies have shown that acute migraine agents work best when used early to treat mild headache[19] and that patients often delay taking their medication for fear of AE.[20]

Whereas individual studies may have particular limitations, e.g. the lack of a placebo arm, the large body of data from these new almotriptan trials supports the role of almotriptan as a first-line agent for the acute treatment of migraine in both triptan-naive and triptan-experienced patients.

5. Conclusions

The findings from these new randomized, double-blind and open-label trials of almotriptan confirm that the high levels of efficacy and tolerability reported for almotriptan in the earlier placebo-controlled clinical trial settings can be achieved in 'real world' clinical settings. The new results are also consistent with previous trials associating almotriptan with an ideal profile for an acute migraine treatment, balancing high efficacy with a low rate of AE. These new trials also demonstrated high levels of satisfaction with almotriptan treatment in both triptan-naive patients and patients dissatisfied with their previous therapy.

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Correspondence and offprints: *Hans-Christoph Diener*, MD, PhD, Department of Neurology, University of Duisburg-Essen, D45122 Essen, Federal Republic of Germany.
Tel: +49 201 723 2460/61; fax: +49 201 723 5901;
e-mail: hans.diener@uni-duisburg-essen.de