Oral Almotriptan vs Oral Sumatriptan in the Abortive Treatment of Migraine

A Double-blind, Randomized, Parallel-Group, Optimum-Dose Comparison

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Background: Almotriptan malate is a novel, selective serotonin_{1B/D} agonist, or triptan, developed for the abortive treatment of migraine. In double-blind, placebo-controlled studies, it has been shown to be effective, well tolerated, and safe.

Objective: To compare the efficacy, tolerability, and safety of almotriptan with that of the “standard triptan,” sumatriptan succinate. The power calculation of the study was based on 24-hour headache recurrence, an efficacy measure in the abortive treatment of migraine, and on the occurrence of adverse events.

Subjects and Methods: Subjects, aged between 18 and 65 years, with migraine with or without aura but otherwise healthy, were randomized to take orally either almotriptan malate, 12.5 mg, or sumatriptan succinate, 50 mg. The medications were provided in identical-looking capsules to ensure blinding and were taken for the treatment of moderate or severe headache. Efficacy was determined in terms of (1) headache relief—a decrease in pain intensity to mild or no pain; (2) headache freedom—a decrease to no pain; (3) use of rescue medications, allowed after 2 hours; and (4) headache recurrence—moderate or severe pain returning within 24 hours after headache relief at 2 hours. Adverse events were collected for 96 hours after treatment and for safety evaluation, vital signs, blood tests, and electrocardiograms were performed at the screening and exit visits.

Results: Seventy-five investigators enrolled 1255 subjects of whom 1173 were treated (591 with almotriptan and 582 with sumatriptan). At 2 hours, almotriptan treatment provided headache relief in 58.0% of the subjects and sumatriptan treatment in 57.3%; headache freedom was provided by the medications in 17.9% and 24.6%, respectively (P = .005). Rescue medications were taken by 36.7% of the subjects in the almotriptan-treated group and by 33.2% in the sumatriptan-treated group; headaches returned to moderate or severe intensity in 27.4% and 24.0%, respectively. Treatment-emergent adverse events occurred in 15.2% of the subjects in the almotriptan-treated group and in 19.4% in the sumatriptan-treated group (P = .001), including chest pain, which occurred in 0.3% and 2.2%, respectively (P = .004).

Conclusions: Almotriptan and sumatriptan are similarly effective in the abortive treatment of moderate or severe migraine headache; they are also similarly well tolerated and safe.

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Almotriptan malate is a novel, selective serotonin_{1B/D} agonist, or triptan, developed for the abortive treatment of migraine. In double-blind, placebo-controlled studies, it has been shown to be effective, well tolerated, and safe. It has a high bioavailability of approximately 80% and has been shown to provide consistent benefit across 3 attacks. On the basis of dose-range studies, its optimum oral dose has been determined at 12.5 mg; it has been studied in doses ranging from 5 to 150 mg. The 12.5-mg dose is the highest effective dose of the medication with placebo-level adverse events. Low occurrence of adverse event, is important in the context of patient satisfaction and treatment compliance.

In this double-blind, randomized, parallel-group study, we compared oral almotriptan malate, 12.5 mg, with oral sumatriptan succinate, the first triptan on the market, in its optimum dose of 50 mg. Apart from the standard outcome measures related to efficacy, tolerability, and safety, we also determined patient satisfaction as well as the effect of treatment on quality of life and health economic outcomes. However, the results of the latter aspects of the study will be published elsewhere.
PATIENTS AND METHODS

STUDY POPULATION

Men and women were eligible for the study if they were between 18 and 65 years, suffered from migraine with or without aura, as defined under codes 1.2 and 1.1, respectively, by the International Headache Society (IHS), and were otherwise healthy. They had to be of sound mind; able to read and understand the informed consent form, written in English; able to comply with the requirements of the study; and voluntarily consent to it. They had to have had a history of migraine headaches for at least 6 months, with an onset before the age of 50 years, and no history of head or neck trauma within the preceding 6 months. They also had to have had an average of at least 2 moderate or severe migraine headaches per month during the preceding 3 months, with an interval of at least 24 hours between consecutive attacks. The subjects could not suffer from migraine with prolonged aura (IHS code 1.2.2), migrainous infarction (IHS code 1.6.2), hemiplegic (IHS code 1.2.3), or basilar migraine (IHS code 1.2.4). Subjects were allowed to have other than migraine headaches, for example, tension or sinus headaches, but had to be able to distinguish between them and their migraine headaches. Women were required to be either menopausal or agree to avoid pregnancy and not be nursing for the duration of the study. The nonmenopausal women had to have used a reliable method of contraception for at least 2 months before enrolling in the study. In addition, they had to have a negative result for a serum pregnancy test at screening and at day 30 of the study, if applicable. Also at screening, they were required to have a clinically acceptable physical examination, blood tests, and electrocardiogram (ECG); the ECG was considered clinically unacceptable if the corrected QT interval was longer than 450 milliseconds for men or 470 milliseconds for women. Exclusion criteria included the following: the subjects could not have uncontrolled hypertension, defined as a diastolic blood pressure higher than 95 mm Hg or a systolic blood pressure higher than 160 mm Hg, or clinically significant disease affecting any system but especially the cardiovascular or gastrointestinal tract. They could not have (a history of) gastrointestinal disease or surgery that would affect the absorption of medications taken orally and had to be mentally stable, without significant psychiatric disease, or have a history of substance abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, within the preceding year. They also could not be using opioids or tranquilizers to the extent that, in the investigator’s opinion, it would interfere with the determination of the efficacy, tolerability, or safety of the study medications. Preventive migraine treatment was allowed with the exclusion of monoamine oxidase inhibitors, lithium carbonate, cyproheptadine hydrochloride, methysergide maleate, ergotamine tartrate, and dihydroergotamine mesylate; taking of these medications had to be discontinued at least 2 weeks before enrollment. Subjects who were triptan naive were also excluded from the study, as well as those with hypersensitivity to or contraindications for the use of triptans, in particular sumatriptan, or ergots, that is, ergotamine and dihydroergotamine. They also could not have had exposure to almotriptan or have participated in an investigational drug or device study within 1 month before screening.

STUDY DESIGN

The subjects completed a screening visit, which included a headache and medical history, physical examination, blood tests, and ECG, and returned 7 to 10 days later for the enrollment visit, if still eligible. They were randomized per investigator and in blocks of 4 to take a single oral dose of almotriptan malate, 12.5 mg, or sumatriptan succinate, 50 mg, provided in identical-looking capsules to ensure blinding, for migraine headache with pain of moderate or severe intensity. They were followed up by keeping a 48-hour diary after taking the study medication and had to return for the exit visit approximately 24 hours later for evaluation of adverse events. They had to treat a migraine headache within 60 days of screening and the women who had not treated a headache by day 30 had to have another serum pregnancy test. The subjects were allowed rescue medications, excluding a triptan or ergot, 2 hours after taking the study medication if the migraine pain had not decreased to mild or none. They were allowed to take the second dose of the study medication if, after relief at 2 hours as specified above, the pain returned at moderate or severe intensity within 24 hours of treatment. They were requested to record the appropriate information in the diary at baseline and at 0.5, 1, 2, 4, 24, and 48 hours after taking the first dose of study medication.

SAFETY ASSESSMENT

At the exit visit, the subjects were asked about any health problems they had experienced since taking the study medication, which were recorded whether or not they were considered by the investigator to be related to the study. However, migraine-related symptoms, that is, headache, nausea, vomiting, photophobia, and phonophobia, were not recorded as health problems and, therefore, not as adverse events unless they were worse than usual. An adverse event

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was considered serious if it (1) was fatal or life-threatening, that is, resulted in an immediate risk of death; (2) was permanently or substantially disabling; (3) resulted in or required intervention to prevent permanent impairment or damage to the body; (4) required hospitalization or a prolonged hospitalization; or (5) was a congenital abnormality or birth defect. The adverse events were classified as mild when they did not interfere with normal functioning, moderate when they interfered somewhat with normal functioning, or severe when they interfered significantly with normal functioning.

**Efficacy Assessment**

Subjects assessed the intensity of migraine pain at baseline as moderate or severe and at 0.5, 1, 2, 4, 24, and 48 hours after taking the study medication as none, mild, moderate, or severe. In doing so, they were asked to use the following guideline: mild pain allows normal functioning; moderate pain inhibits but does not prohibit normal functioning and does not require bed rest; severe pain prohibits normal functioning or requires bed rest. Headache relief was defined as a decrease in pain intensity from moderate or severe at baseline to mild or no pain at the time of postbaseline assessment; those subjects who achieved this degree of headache relief at 2 hours were considered responders. Headache freedom was defined as a decrease in pain intensity from moderate or severe at baseline to no pain at the time of postbaseline assessment. Rescue medications were allowed 2 hours after taking the first dose of the study medication and was defined as any medication taken for pain relief. Recurrence was defined as an increase in pain intensity to moderate or severe within 24 hours after taking the first dose of the study medication, after relief to mild or no pain at 2 hours.

The primary efficacy determination was headache relief at 2 hours after taking the first dose of study medication; headache freedom was also assessed. In addition, efficacy of the study medication for headache relief and headache freedom was determined at 0.5 and 1 hour after taking the first dose of the study medication and recurrence at 24 hours. The degree to which the migraine-associated symptoms, that is, nausea, vomiting, photophobia, and phonophobia, troubled the subjects was recorded at baseline and at 0.5, 1, and 2 hours only, in terms of not having the symptom at all or being not, slightly, moderately, very, or extremely bothered by it.

**Statistical Analysis**

Efficacy data were analyzed using an intent-to-treat approach in which all randomized subjects were included who experienced moderate or severe migraine headache, took at least 1 dose of study medication, and had at least 1 postbaseline efficacy assessment. Carrying the last recorded observation forward whenever this was possible was used to impute missing data, and a difference with a P value of .05 was considered statistically significant.

The proportion of subjects in each of the 2 treatment groups experiencing headache relief or headache freedom at 0.5, 1, and 2 hours were compared using the χ² or Fisher exact test. We also compared the proportion of those subjects experiencing recurrence of moderate or severe pain within 24 hours and the proportion using rescue medications. Analyses adjusting for baseline pain intensity were performed using the Cochran-Mantel-Haenszel test; subgroup analyses were performed by sex as well.

Safety data were also analyzed using an intent-to-treat approach in which all randomized subjects were included who experienced moderate or severe migraine headache and took at least 1 dose of the study medication. The primary safety end point was that of treatment-emergent adverse events, which includes all adverse events whether or not they were considered to be related to the study medications. The adverse events were tabulated by body system and by disorder within each body system. They were compared between the treatment groups by body system and by selected disorders, using the χ² or Fisher exact test.

**Power Calculation**

The power of the study was calculated on the basis of the 24-hour headache recurrence and occurrence of adverse events. On the basis of prior studies, it was assumed that the 24-hour headache recurrence would be 25% for almotriptan malate, 12.5 mg, and 35% for sumatriptan succinate, 50 mg. With the use of a 2-sided test and a of .05, a sample of 329 responders in each group was calculated to provide a power (1−β) of 0.80, to detect this difference as statistically significant. It was projected that 70% of the enrolled subjects would, in fact, take study medication within the 60 days allotted and that 70% of them would respond to it, in terms of headache relief at 2 hours. Therefore, 660 subjects were thought to be required in each of the 2 treatment groups to obtain 329 responders in each, making a total of 1320 for the whole study. Of the 1320 subjects, 924 would then be evaluable for efficacy analysis because they took the study medication within the allotted time. Information about adverse events gathered from previous studies suggested overall rates of 11% for almotriptan malate, 12.5 mg, and 20% for sumatriptan succinate, 50 mg. The power (1–β) to detect this difference as statistically significant given a total sample size of 924, that is, 462 per treatment arm, was more than 0.95.

Of the 591 subjects who took almotriptan, 65 (11.0%) were men and 526 (89.0%) were women; exactly the same sex distribution was seen in the 582 subjects who took sumatriptan (64 [10.9%] were men and 518 [89%] were women). Their mean (±SD) ages were 41.2±10.1 years and 40.3±10.1 years, respectively. Of those in the almotriptan-treated group, 94.9% were white, 3.9% black, and 1.2% other; these numbers were 94.7%, 4.0%, and 1.4%, respectively, for the sumatriptan-treated group. The only statistically significant difference between the 2 groups in terms of demographics was body weight: the subjects in the almotriptan-treated group had a mean weight of 74.5 kg and those in the sumatriptan-treated group, 72.3 kg (P = .003).

**Baseline Migraine Characteristics**

The baseline migraine characteristics, that is, pain, nausea, vomiting, photophobia, and phonophobia, for the 2 treatment groups are listed separately in Table 1. In both treatment groups, the baseline pain intensity was severe...
in approximately 33% of the subjects, with a slightly lower proportion of men in comparison to women having severe pain. The occurrence of migraine-associated symptoms in both treatment groups was in agreement with what is generally seen in clinical studies. In Table 1, subjects who did not have the symptom or were not bothered by it were classified as not having the symptom; they were classified as having the symptom if they were slightly, moderately, very, or extremely bothered by it.

### Efficacy

The efficacy of the study medications for headache relief and headache freedom, as defined earlier, for the first 2 hours of the study are shown in Figure 2. Almotriptan provided headache relief at 2 hours in 58.0% of the subjects, compared with 57.3% for sumatriptan; for headache freedom at 2 hours, the percentages were 17.9% and 24.6%, respectively. The differences between the 2 study medications at 0.5, 1, and 2 hours were not statistically significant, except for headache freedom at 2 hours in favor of sumatriptan ($P = .005$). Adjusting for baseline pain intensity did not alter the results and neither did the determination of efficacy for moderate and severe pain separately and for men and women separately.

The results of the study with regard to the migraine-associated symptoms—nausea, vomiting, photophobia, and phonophobia—are shown separately for the almotriptan-treated and sumatriptan-treated groups (Figure 3). If a subject was slightly, moderately, very, or extremely bothered by an associated symptom, that subject was classified as having the particular symptom, as opposed to not having it or not being bothered by it. The differences between the 2 medications in reducing the migraine-associated symptoms—nausea, vomiting, photophobia, and phonophobia—were not statistically significant.

Rescue medications were taken by 36.7% of the subjects in the almotriptan-treated group and by 33.2% in the sumatriptan-treated group. Of the 343 responders in the almotriptan-treated group, 27.4% experienced recurrence of moderate or severe headache within 24 hours, as compared with 24.0% of the 333 responders in the sumatriptan-treated group. The differences were not
statistically significant and adjusting for baseline pain intensity did not affect these results. No statistically significant differences were noted between the 2 treatment groups for recurrence, when determined for moderate and severe pain separately and for men and women separately.

TOLERABILITY AND SAFETY

The frequency of occurrence of treatment-emergent and treatment-related adverse events for the 2 groups is shown separately in Figure 4. There were no serious adverse events in either group and no subject discontinued treatment prematurely because of adverse events. The difference between the 2 groups for treatment-emergent adverse events was almost statistically significant (P = .06); the difference for the treatment-related adverse events was statistically significant in favor of almotriptan (P = .001).

Table 2 lists the treatment-emergent adverse events that occurred in at least 1% of the subjects in either treatment group. The most common adverse events were nausea, dizziness, and somnolence; the difference between the 2 groups for chest pain was statistically significant for the almotriptan-treated group (P = .004). Finally, with regard to safety, the treatment-emergent adverse events that involve the cardiovascular system are summarized in Table 3. The occurrence of these adverse events was very low in both treatment groups. Also, there were no changes observed in the vital signs, blood test results, and ECGs as recorded at screening and at the exit visits, approximately 96 hours after taking the study medication.

ADJUSTMENTS FOR MULTIPLE COMPARISONS

As mentioned, the difference between the almotriptan-treated and sumatriptan-treated groups for chest pain was statistically significant.
statistically significant ($P = .004$). However, there were 18 other treatment-emergent adverse events that were reported by enough subjects to make it possible for the events to be statistically significantly different between the 2 treatment groups, but none of them were. Nevertheless, if there was, indeed, no difference between the 2 groups for treatment-emergent adverse events, the probability of at least 1 of the 19 comparisons emerging as statistically significant may be much greater than .05. To adjust the chest pain–related $P$ value for the other 18 treatment-emergent adverse events, a bootstrap resampling simulation approach was used. Unlike the Bonferroni correction for multiple comparisons, this approach considers the correlation between the comparisons. In 2548 of the 100000 simulated sets performed on the 1173 treated subjects, the $P$ value for at least 1 of the 19 comparisons was less than .004. This makes the adjusted $P$ value for the chest pain comparison between the 2 treatment groups .03, that is, it remains statistically significant even after the adjustment.

A similar simulation approach was used to adjust the $P$ value of the almotriptan-sumatriptan comparison for headache freedom at 2 hours, to account for the other 5 other comparisons related to headache relief and headache freedom at 0.5, 1, and 2 hours. The adjusted $P$ value was .03, which means that after the adjustment, the comparison between the 2 treatment groups for headache freedom at 2 hours also remained statistically significant.

### COMMENT

In this double-blind, randomized, parallel-group study comparing almotriptan malate, 12.5 mg, with sumatriptan succinate, 50 mg, both administered orally, the 2 medications were found to be similarly effective in providing relief of migraine headache. Sumatriptan has been available for a decade and has become the standard in abortive migraine treatment, prompting the comparison with almotriptan. It has an extensive efficacy, tolerability, and safety record and, therefore, lends itself well as a comparator for a novel medication in the same class. Its optimum oral dose has been determined at 50 mg, which is the lowest dose with maximum therapeutic benefit and the highest effective dose with placebo-level adverse events. In this study, it was compared with the optimum oral dose of almotriptan, which has been determined to be 12.5 mg and is the highest effective dose of the medication with placebo-level adverse events. With regard to almotriptan, prior studies have also shown a particularly good duration of action of the medication, resulting in a relatively low 24-hour headache recurrence of approximately 25%.

A total of 1173 subjects were treated in the study with no significant differences between the 2 treatment groups for sex, age, race, and baseline migraine characteristics. There was a statistically significant difference between the 2 treatment groups for body weight, with the subjects in the almotriptan-treated group on average being heavier than the subjects in the sumatriptan-treated group. They also experienced nausea at baseline more frequently than those in the sumatriptan-treated group, but the difference was just above the level of statistical significance. Despite these differences to the disadvantage of almotriptan, the 2 medications proved similarly effective as determined by headache relief at 0.5, 1, and 2 hours after treatment and headache freedom at 0.5 and 1 hour.

The extent to which rescue medications were taken, allowed 2 hours after treatment, was the same in the almotriptan-treated and sumatriptan-treated groups, that is, approximately 35%. The same was true for the 24-hour headache recurrence, which was approximately 25% in both treatment groups. For adverse events, nothing serious was encountered in the study and no subjects discontinued treatment prematurely because of them. The occurrence of treatment-emergent adverse events was the same in both groups (15%-20%). However, treatment-related adverse events occurred more than one third less often in the almotriptan-treated group than in the sumatriptan-treated group, a difference that was statistically significant. In addition, chest pain reported by the subjects after taking study medication was only a fraction in the almotriptan-treated group of what it was in the sumatriptan-treated group.

The triptans, a pharmacological group to which both almotriptan and sumatriptan belong, are potent arterial vasoconstrictors. They exert their vasoconstrictor effect through stimulation of the serotonin $\mathrm{\text{tr}}$ receptor for which they have a high selectivity. The serotonin $\mathrm{\text{tr}}$ receptor is present particularly on the cranial, including the extracranial, arteries and to a much lesser extent on those in the coronary circulation, where the serotonin $\mathrm{\text{tr}}$ receptor predominates. As a result, the vasoconstriction exerted by the triptans on the coronary arteries is only about one fourth of that exerted on the cranial arteries and, in clinically relevant concentrations, is close to negligible. Nevertheless, coronary vasoconstriction is a concern with the triptans, which is also the reason that uncontrolled hypertension and coronary artery disease are considered contraindications for their use.

Chest pain can be a manifestation of coronary vasoconstriction; however, it was also found to occur with a compound that is devoid of vasoconstrictor activity but shares with the triptans high affinity for the neuronal serotonin $\mathrm{\text{tr}}$ receptor. As stated earlier, the occurrence of chest pain was only a fraction in the almotriptan-treated group of what it was in the sumatriptan-treated group, emphasizing the better tolerability of almotriptan. As the relationship of chest pain to coronary vasoconstriction is far from clear, extrapolation to safety is, therefore, unwarranted. However, no safety issues emerged in the study in which almost 1200 subjects were treated, half with almotriptan and half with sumatriptan, and were followed up for up to 96 hours after treatment, with the inclusion of vitals signs and ECGs.

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