Almotriptan in the treatment of migraine

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Abstract: Almotriptan is an orally administered, highly selective serotonin 5-HT(1_B/1_D) receptor agonist that is effective in the acute treatment of moderate to severe migraine attacks. Since its introduction on to the market in 2001, several studies involving a large number of migraine patients have confirmed its efficacy and tolerability profile. Almotriptan, was found to be among the best-responding triptans in terms of pain relief and pain-free rate at 2 h. It has been reported that almotriptan has the best sustained pain-free (SPF) rate and the lowest adverse events (AEs) rate of all the triptans. When these clinical characteristics were combined to form the composite endpoint SPF and no AEs (SNAE), almotriptan emerged as the triptan with the best efficacy and tolerability profile. It also showed a good efficacy profile during the early treatment (within 1 h of onset) of migraine attacks characterized by moderate pain intensity. On the basis of these findings, almotriptan may be considered a therapeutic option for the acute treatment of migraine attacks.

Keywords: almotriptan, triptans, migraine, treatment

Introduction

Migraine is a very common chronic and sometimes progressive (Lipton and Pan 2004) neurological disorder, characterized by recurrent attacks of pulsating headache with or without aura, aggravated by physical activity and associated with vegetative symptoms (eg, sensitivity to light and noise, nausea, and vomiting) (IHS 2004). It affects women three times more frequently than men, and the majority of sufferers are aged between 25 and 55 years, which are usually an individual's most productive and socially active years (Lipton and Bigal 2005).

In a World Health Organization (WHO) report in 2000 (Mathers et al 2002), migraine was ranked 19 among disorders causing years lived with a disability for both sexes (and 9 when considering only women), and the level of disability during a severe migraine attack is considered to be on a par with that associated with active psychosis, tetraplegia and dementia.

The estimated mean prevalence of migraine in Europe is 16.6% in women and 7.5% in men (Stovner et al 2006); in the US, the corresponding figures are 18.2% and 6.5% (Lipton et al 2001). Because of its peculiar clinical and epidemiological features, migraine places a significant economic burden on society, estimated (in terms of reduced productivity and missed workdays) to amount, annually, to €27 billion in the European Community (Andlin-Sobocki et al 2005) and $13 billion in the US (Hu et al 1999). The pathophysiology of migraine is linked, essentially, to a genetic component and to peripheral activation of the ophthalmic branch of the trigeminal nerve, probably caused by neurogenic plasma protein extravasation and neuropeptide release (so-called neurogenic inflammation) (Markowitz et al 1987; Moskowitz 1990), as well as to activation of second order neurons on the superficial lamina of the trigeminal nucleus caudalis (Goadsby and Zagami 1991), as hypothesized after animal studies.

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In both neurogenic inflammation and central sensitization of the trigeminal nerve it has been demonstrated, through the activity of different subtypes of serotonin receptor, such as 5-HT_{1B}, which is responsible for vasoconstriction and inhibition of neurogenic inflammation (Buzzi and Moskowitz 1990; Yu et al 1996), and 5-HT_{1D}, responsible for inhibition of trigeminal neuronal activation (Storer and Goadsby 1997), that serotoninergic transmission plays a pivotal role. This led to the synthesis and development of 5-$HT_{1B/1D}$ receptor agonists, the triptans, for the treatment of migraine attacks.

According to American and European practice guidelines (Silberstein 2000; EFNS task force 2006), and as confirmed by a survey of acute migraine sufferers (Lipton et al 2002), the outcome measures of acute migraine treatment considered most important are rapid onset of efficacy, complete pain relief without recurrence, reduced need for rescue medication, and no adverse events (AEs). More recently, in order to represent more accurately what migraine patients want from their acute migraine therapy, composite endpoints encompassing the measures able to predict patient satisfaction (such as pain-free state, use of rescue medication, AEs) have been developed and introduced (Sandrini et al 2005).

In recent years the triptans have become the recommended drugs for the acute treatment of moderate and severe migraine attacks, and in patients who failed to respond to non-specific agents (Silberstein 2000), on account of their very favorable efficacy and tolerability profile.

Seven triptans are currently available for the treatment of acute migraine (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan) and they have been found to show a significant variability in terms of their efficacy and tolerability.

Almotriptan, which several studies have shown to be effective and tolerable, represent a first-line treatment for acute migraine attacks.

Pharmacology

Binding and in vitro studies have shown that almotriptan (3-[2-dimethylamino ethyl]-5-(pyrrolidin-1-ylsulfonylmethyl)-1H-indole) is a potent and selective 5-HT($1_B/1_D$) receptor agonist. It has high affinity (in the low nM range) and high selectivity for serotonin 5-HT human cloned receptor $1_B/1_D$ and for those in animal tissues (Bou et al 2000), but lower affinity for all the other serotoninergic receptors. Its affinity for 5-HT_{1A} receptors is more than 60-fold lower than its affinity for 5-$HT_{1B/1D}$ receptors, and about 40-fold lower than its affinity for 5-HT_7 receptors. Similarly, significant affinity was found for 5-HT_6 receptors, although the clinical potential of 5-HT_6 and 5-HT_7 receptor ligands is still unknown (Bou et al 2000). Almotriptan has been studied in human cloned transfected 5-HT_{1F} receptors, for which it also shows significant affinity, about 20 nM (Bou et al 2000).

As regards its action, it has been postulated that almotriptan, like other triptans, induces both vasoconstriction, by acting on the 5-HT_{1B} receptor subtype, and inhibition of nociceptive transmission, via 5-HT_{1D} receptor interaction (Bou et al 2001; Hoskin et al 2004).

When the contractile effect of almotriptan and sumatriptan was studied in preparations of isolated vessels from the human brain (meningeal, temporal, basilar and internal carotid arteries), coronary arteries and other vascular beds, almotriptan showed a superior potency and efficacy in contracting the meningeal artery compared to sumatriptan, and a similar efficacy to sumatriptan on cranial vessels that are not directly involved in migraine pathophysiology and on extracranial vessels. On the contrary, almotriptan dislayed a lower contractile effect compared to sumatriptan on vessels (ie, coronary arteries) suggested to be related to AEs associated with the triptans (Bou et al 2001). Almotriptan (0.3 mg/kg) inhibits the extravasation of plasma from dural vessels following trigeminal ganglion stimulation, exerting an action similar to that of sumatriptan (1 mg/kg) (Gras et al 2000). Inhibition of nociceptive transmission by activating the 5-HT_{1D} receptors in peripheral trigeminal sensory nerve terminals in the meninges and central terminal in brain stem sensory nuclei, as demonstrated for other triptans (Hoskin et al 2004), can be hypothesized for almotriptan, too, and could explain not only its efficacy on pain transmission at brainstem level, but also its effect on the associated symptoms, including nausea and vomiting.

The bioavailability of almotriptan after oral administration is approximately 70% (Jansat et al 2002), similar to that of naratriptan, but significantly higher than the range reported for the other triptans (14%–50%) (Jhee et al 2001). Absorption is rapid, maximal plasma concentration is achieved between 1.5 and 4 h after dose administration; however, after 1 h the plasma concentration is 68% of the Cmax (Fleishaker, Ryan, Carel et al 2001).

The mean half-life ranges between 3 and 5 h (McEnroe and Fleishaker 2005), in line with other triptans but significantly lower than the 25 h half-life of frovatriptan (Tfelt-Hansen et al 2000). Almotriptan is largely distributed in body fluids with a volume of distribution, after intravenous administration, of 1951; as with other triptans, its protein

binding does not reach 40% (Gras et al 2002). Almotriptan is eliminated, mainly in urine (75%) but also in feces (12%), within 1 week of administration, although more than half of the dose administered is eliminated within the first 6 hours (McEnroe and Fleishaker 2005). Almotriptan is metabolized in vivo primarily via oxidation by monoamine oxidase-A and then by cytochrome P450 (CYP) (3A4 and 2D6 isoenzymes) and flavin monooxygenase in three compounds: indolacetic acid and its glucuronide conjugate and the oxidized pyrrolidine product (Jansat et al 2002). Around 30%–40% of the dose is excreted in the urine unchanged, 27% is metabolized by monoamine oxidase-A, and a small percentage is metabolized by CYP. Since urinary excretion is the primary route of elimination, renal function is the factor that most conditions almotriptan clearance, followed by enzymatic metabolism. On this basis, some authors recommend that the dosage be limited to 1 tablet/24 h in migraine patients with severe renal disease (Dodick 2003). Hepatic impairment, even when severe, does not appear to affect the pharmacokinetic parameters much more than impaired renal function does, and in this situation, too, 1 tablet/24 h is recommended as the maximum daily intake (McEnroe and Fleishaker 2005). The fasted or fed condition has not been found to modify significantly the bioavailability profile or the therapeutic effect of almotriptan (Jansat et al 2006).

Almotriptan has been tested for its potential pharmacokinetic interaction with several drugs, including MAO-A inhibitors (Fleishaker, Ryan, Jansat et al 2001), SSRIs (Fleishaker, Ryan, Carel et al 2001), β-adrenergic (Fleishaker, Sisson et al 2001) and calcium channel blocking agents (Fleishaker et al 2000), and ketokonazole (Fleishaker et al 2003), and even though some pharmacokinetic interaction was shown, including an increased plasma concentration of almotriptan, the authors did not find a clinically significant profile. Consequently, no dose adjustment is necessary when almotriptan is taken together with these drugs. On the contrary, the recommendation to wait for at least 24 h before taking a triptan following administration of any ergotamine-containing preparation is still valid.

The pharmacokinetic characteristics of almotriptan are given in Table 1.

Table 1 Pharmacokinetic characteristics of almotriptan

Treatment characteristics	Almotriptan
5-HT receptor affinity	I_B/I_D
T_{max} (h)	1.5–2.0
Half-life (h)	3–5
Bioavailability (%)	70
Volume of distribution (l)	195
Metabolism	MAO-A CYP450
Elimination	Renal (75%)
Elimination renal inactive (%)	50
Lipophilicity	low
CNS side effects (%)	–1.5

Clinical efficacy

The clinical efficacy and tolerability of almotriptan has been tested in two controlled, double-blind, randomized clinical trials against placebo (Pascual et al 2000; Dahlof et al 2001) and in two trials (Spierings et al 2001; Dowson et al 2002) that also included sumatriptan. Together, these four trials included 2500 patients who met the International Headache Society (IHS) criteria for moderate-to-severe acute episodic migraine.

In the first trial (Pascual et al 2000), the 722 patients who completed the study received a single dose of placebo, almotriptan 6.25 mg, or almotriptan 12.5 mg during three consecutive migraine attacks of moderate or severe intensity.

The primary endpoint was the number of migraine attacks out of the three, in which there was pain relief (pain reduced from moderate or severe to mild or no pain) at 2 h after intake. A consistent response was achieved across and within patients for almotriptan, 6.25 or 12.5 mg, compared with placebo (pain relief within 2 h in at least two out of three attacks in 64% and 75% vs 36% of patients, respectively). Similarly, pain relief at 2 h was found to be significantly higher ($p < 0.001$) after treatment with almotriptan, 6.25 (60%) or 12.5 mg (70%), compared with placebo (38%) (Table 2). The number and percentage of attacks, out of the three, that were pain-free at 2 h, without use of rescue medication, were significantly higher ($p < 0.001$) after almotriptan, 6.25 (29.9%) and 12.5 mg (38.8%), than after placebo (15.5%) (Table 2). In terms of onset of action, almotriptan 6.25 mg (30.1%) and almotriptan 12.5 mg (34.5%) both showed a significant ($p < 0.001$) percentage increase in the number of attacks in which relief was obtained after 1 h compared with placebo (21.6%), and almotriptan 12.5 mg (12.5%) was also significantly ($p < 0.01$) more efficacious than both almotriptan 6.25 mg (7.3%) and placebo (5.7%) in producing pain-free state 1 h after treatment. Three of the migraine-related symptoms considered (phonophobia, photophobia and vomiting) improved significantly (all $p < 0.01$) following almotriptan 12.5 mg as opposed to placebo intake. No significant differences in terms of relapses were found when almotriptan 12.5 mg (30.1%) and 6.25 mg (28.7%) were compared with placebo (23.3%). Nearly a quarter (23.1%) of patients experienced an AE. The AE rate decreased from the

Table 2 Data from clinical trials of almotriptan

	No. of patients	Pain relief 2 h (%)	Pain-free 2 h (%)		
Pascual et al 2000					
Placebo	176	38.4	15.5		
Almotriptan 6.25 mg	360	59.9*	29.9*		
Almotriptan 12.5 mg	373	70.3*	38.8*		
Dahlof et al 2001					
Placebo	80	32.5	11.3		
Almotriptan 2 mg	170	30	17.1		
Almotriptan 6.25 mg	167	56.3*	30.0*		
Almotriptan 12.5 mg	164	58.5*	37.8*		
Almotriptan 25 mg	161	66.5*	45.3*		
		Stratified for baseline pain level			
Dowson et al 2002		**moderate**	**severe**	**moderate**	**severe**
Placebo	99	46.3	34.4	16.4	12.5
Almotriptan 12.5 mg	184	72.0	41.1	38.7	16.7
Almotriptan 25 mg	191	66.7	44.2	46.7	19.8
Sumatriptan 100 mg	194	73.9	50.0	36.9	29.3
Spierings et al 2001					
Almotriptan 12.5 mg	591		58.0		17.9
Sumatriptan 50 mg	582		57.3		24.6**

*statistically significant difference ($p < 0.001$) when compared with placebo.
**statistically significant difference ($p < 0.05$) when compared with almotriptan.

first to the third attack and there were no significant differences between the groups in the percentages of AEs.

A dose-finding, placebo-controlled, double-blind, parallel-group, phase II study (Dahlof et al 2001) investigated 742 migraineurs who were randomized to a single dose of placebo or oral almotriptan (2, 6.25, 12.5, or 25 mg) and instructed to treat when pain was moderate or severe.

The number of patients with headache response at 2 h, defined as a decrease from severe or moderate pain at baseline to mild or no pain 2 h after study treatment without the use of escape medication, was the primary endpoint. The patients with headache response at 2 h were 32.5% after placebo, and 30.0%, 56.3%, 58.5%, and 66.5% after almotriptan 2, 6.25, 12.5, and 25 mg respectively (Table 2) showing a significant dose dependent increase ($p < 0.0001$). The doses from 6.25 to 25 mg demonstrated greater efficacy compared with placebo ($p < 0.001$), without significant differences emerging in response at 2 hours between the doses in this range.

The percentages of patients who were completely pain-free within 2 h of almotriptan ingestion were 37.8% and 45.3% in the 12.5-mg and 25-mg treatment groups, compared with 11.3% in the placebo group. Moreover, all the doses of almotriptan showed significantly higher percentages of pain-free patients at 1, 1.5, and 2 h compared with placebo. The percentages of associated symptoms (nausea, vomiting, phonophobia, and photophobia) tended to improve in a dose-dependent manner (all $p < 0.001$), even though the majority of patients reported these symptoms as unchanged. AEs were experienced by 18.7% of the randomized patients, and the incidence and intensity of these AEs were dose-dependent, reaching significance at the 25 mg dose (which was also the dose at which more patients experienced AEs whose severity they considered moderate). On contrary, the incidence of AEs at all other doses of almotriptan was similar to that found in the placebo group. On the basis of these efficacy and tolerability data the authors suggest that 12.5 mg is the optimal dose of almotriptan.

In the randomized, single-dose, double-blind, parallel-group, placebo-controlled, multicenter clinical study by Dowson et al (2002), almotriptan, 12.5 and 25 mg, was compared with sumatriptan 100 mg. A total of 668 patients treated one migraine attack of moderate or severe intensity with the study medication. Pain relief at 2 h after treatment (defined as improvement from severe or moderate pain to mild or no pain at 2 h after treatment) was the primary endpoint. The response rates for moderate or severe pain were 56.8% after almotriptan 12.5 mg, 56.5% after almotriptan 25 mg, and 63.7% after sumatriptan, all three active treatments thus giving significantly better results than the placebo, which recorded a response rate of 42.4%. Considering pain relief at 2 h stratified by intensity of the attack (moderate or severe), almotriptan (both doses) and sumatriptan both showed a

significantly better response than placebo, with sumatriptan 100 mg giving better results than almotriptan (Table 2).

When the secondary endpoint "pain-free at 1 h and 2 h" was stratified by intensity of the pain (moderate or severe), the authors found that, among the patients reporting moderate pain, the rates of pain-free responses at 2 h were considerably higher in both the almotriptan (38.7% for the 12.5 mg; 46.7% for the 25-mg dose) and the sumatriptan (36.9%) groups (almotriptan 25 mg giving the best results) than in the placebo group (16.4%); the pattern was similar in the patients reporting severe pain (albeit based on less evidence and with the best response found in the sumatriptan group) (Table 2). On the contrary, when considering only the pain-free at 1 h endpoint, the tested drugs showed a better response than the placebo (almotriptan 25 mg giving the best results) only in the patients reporting moderate pain, while in those with severe pain the drugs and placebo gave similar results.

The recurrence rate after 24 h in patients treating severe pain was significantly lower after treatment with almotriptan 12.5 mg (8.8%) and 25 mg (16.2%) than after treatment with either sumatriptan (28.9%) or placebo (27.3%). While no differences were found in the recurrence rate between the groups when moderate pain was treated (almotriptan 12.5 mg = 22.7%, almotriptan 25 mg = 14.9%, sumatriptan = 22.4%, placebo = 16.7%), all three active treatments reduced the incidence of associated symptoms compared with placebo, and also showed a lower rate of recourse to rescue medication (almotriptan 12.5 mg = 38.6%; almotriptan 25 mg = 38.2%; sumatriptan = 32.4%) than placebo (55.5%). This study reported a very low rate of AEs, both for almotriptan and for sumatriptan.

In a large double-blind, placebo-controlled study (Spierings et al 2001), the efficacy, safety and tolerability profile of almotriptan 12.5 mg was compared with that of sumatriptan 50 mg, enrolling 1173 subjects who treated moderate or severe migraine headache. The primary endpoints were pain relief (defined as a decrease in pain intensity from moderate or severe at baseline to mild or no pain at 2 h after treatment) and pain-free state (defined as a decrease in pain intensity from moderate or severe at baseline to no pain at 2 h after treatment) at 2 h. With regard to the first of these, both almotriptan and sumatriptan showed a similar rate (58.0% and 57.3% respectively), whereas sumatriptan 50 mg (24.6%) proved significantly ($p = 0.05$) more efficacious than almotriptan (17.9%) in producing headache freedom at 2 h (Table 2). No significant differences emerged between the two study drugs when the two endpoints were evaluated at 0.5 and at 1 h. Similarly, no differences were found between the capacity of almotriptan 12.5 and sumatriptan 50 mg to reduce migraine-associated symptoms. Rescue medication was used by 36.7% of the almotriptan-treated and by 33.2% of the sumatriptan-treated patients. The recurrence rate within 24 h of a moderate or severe headache was 27.4% after treatment with almotriptan and 24.0% after treatment with sumatriptan, a difference that did not reach statistical significance. Both drugs showed a good tolerability profile and no serious AEs were reported.

A recent meta-analysis (Dahlöf et al 2006) of 4 randomized, placebo-controlled, double-blind clinical trials has produced further significant clinical data in favor of almotriptan. On the basis of this analysis of more than 1900 doses of almotriptan and almost 400 of placebo, it emerged, as early as 30 min after dosing, that almotriptan 12.5 mg was significantly more effective than placebo in producing pain relief (14.9% vs 8.2%; $p < 0.05$) and pain-free state (2.5% vs 0.7%; $p < 0.05$).

The composite endpoint

In a survey of 1660 migraineurs experiencing severe headache or migraine, pain relief and speed of onset were important treatment attributes for more than 75% of sufferers, and the absence of AEs was important to over 40% (Gallagher and Kunkel 2003). It was estimated that AEs caused more than 70% of the patients to delay or avoid taking medication, which had significant negative repercussions on headache intensity and duration and social functioning (Gallagher and Kunkel 2003). For migraineurs, the most important attributes of acute treatments are complete pain relief, lack of recurrence, rapid onset of action, and absence of AEs. A randomized controlled trial of rizatriptan showed that patients who experience complete pain relief and are able to function at their normal levels within 2 h and experience no headache recurrence have the highest migraine-specific quality of life scores (Santanello et al 2002). In the light of these findings, and also in order to better reflect what patients want from their migraine treatment, a composite clinical endpoint has been developed that combines the sustained pain-free (SPF) rate, defined as pain-free at 2 h after medication administration with no recurrence of moderate-to-severe headache and no use of rescue medication from 2 to 24 h post-dose (Tfelt-Hansen et al 2000), with the outcome no AEs (SNAE); this composite endpoint, by including tolerability (Dodick et al 2007), another crucial factor in migraine treatment, is thus an evolution of the SPF.

The SPF rate was considered in a pooled analysis (Dodick 2002) of three randomized, double-blind, placebo-controlled trials evaluating the efficacy of almotriptan. Two studies

Table 3 Patients with sustained pain-free according to baseline pain severity as considered in a pooled analysis of three placebo-controlled trials by Dodick (2002)

	Moderate pain (%)	Severe pain (%)
Placebo	10.2	3.2
Almotriptan 6.25 mg	25.5*	16.2
Almotriptan 12.5 mg	31.3*	17.3*
Placebo	16.1	3.1
Almotriptan 6.25 mg	25.6	21.5*
Almotriptan 12.5 mg	32.0*	20.9*
Placebo	15.0	6.0
Almotriptan 6.25 mg	33.0*	15.0
Sumatriptan 100 mg	31.5*	24.0*

*statistically significant difference ($p < 0.05$) when compared with placebo.

compared almotriptan, 6.25 mg and 12.5 mg, with placebo, and the third almotriptan 12.5 mg and sumatriptan 100 mg.

In all three studies, both the almotriptan (6.25 mg and 12.5 mg) and sumatriptan gave significantly better ($p < 0.05$) SPF rates than placebo. Taking into account the intensity of the baseline pain (moderate or severe pain), among patients with moderate pain almotriptan, 6.25 mg showed a significantly better SPF with respect to placebo in one study (25.5% vs 10.2%, $p < 0.032$) (Table 3), while almotriptan 12.5 mg gave a significantly higher SPF rate than placebo in both the studies (31.3% vs 10.2%, $p < 0.004$ and 32.0% vs 16.1%, $p < 0.002$) (Table 3). Among patients with severe pain, almotriptan 6.25 mg showed a significantly better results than placebo in one study (21.5% vs 3.1%, $p < 0.005$), while, also in this case, almotriptan 12.5 mg resulted significantly better in both the studies (17.3% vs 3.2%, $p < 0.032$ and 20.9%, $p < 0.001$) (Table 3).

In the trial that also considered sumatriptan, the proportion of patients achieving SPF was similar between almotriptan 12.5 mg and sumatriptan 100 mg and significantly higher than that in placebo group. The SPF rates produced by almotriptan 12.5 mg (33.3%) and sumatriptan 100 mg (31.5%) in patients with moderate pain at baseline were similar and significantly higher than those in the placebo group ($p < 0.05$). In patients treating severe pain, sumatriptan 100 mg gave a significantly higher SPF rate than placebo, whereas no significant differences were noted between almotriptan 12.5 mg and placebo (Table 3).

A very interesting clinical profile of almotriptan 12.5mg emerged from a recent analysis (Dodick et al 2007) of the data derived from a large meta-analysis of 53 clinical trials of triptan efficacy and tolerability that evaluated more than 24000 patients (Ferrari et al 2002). The relationship between SPF and AEs was investigated in order to consider the rationale for using the SNAE endpoint in clinical trials. The results showed that higher SPF rates were related to higher AE rates, except after administration of almotriptan 12.5 mg, which showed the lowest AE rate (14.2%; approximately 30% lower than expected) and the highest SPF rate (25.9%), coupled with the highest SNAE rate (22.2%; range 11.7%–25.9%), of the six triptans evaluated (Figure 1).

Early treatment with almotriptan

A growing body of evidence supports the increased efficacy of migraine attack treatment with symptomatic drugs over the conventional approach (until now widely employed in clinical trials), which is to treat when the pain is moderate or severe. This is especially true in the case of the triptans, where early treatment is associated with higher pain-free rates, together with reductions in rescue medication use and recurrence rates (Lainez 2004).

Almotriptan has been evaluated in several retrospective analyses which set out to address the benefits of early intervention, during the mild phase of the attack. In a post-hoc analysis (Pascual and 2002) of a trial involving 762 migraineurs who treated 6 attacks, 3 during mild pain and 3 during moderate or severe pain, the pain-free rate at both 1 h and 2 h post-dose was significantly greater in the patients who treated their attacks when the pain was mild (47% and 84%, respectively) as opposed to moderate or severe (14% and 53% respectively). Also, the consistency of the pain relief (pain-free in at least two out of three attacks) at both 1 h and 2 h was significantly increased in the patients who treated mild pain (45% and 88% respectively) compared to patients who treated moderate or severe pain (14% and 56% respectively). Similarly, both the recurrence rate and the need for rescue medication were significantly lower in those who treated mild pain (28% and 8% respectively) as opposed to moderate or severe pain (33% and 13% respectively).

Another post-hoc analysis (Mathew 2003) was based on a multicenter, open-label, long-term trial (Mathew et al 2002) involving 582 patients who treated 10645 migraine attacks with almotriptan 12.5 mg. Treatment when pain was mild gave significantly higher pain-free rates at both 1 h ($p < 0.001$) and 2 h ($p < 0.001$) (35.3% and 76.9% respectively) compared to treatment when pain was moderate or severe (7.5% and 43.9% respectively). The recurrence rate and use of rescue medication were also significantly lower (both $p < 0.001$) in the patients who treated their attacks when the pain was mild (12.9% and 9.4% respectively) as opposed to moderate or severe (25.0% and 17.2% respectively). The SPF rate in

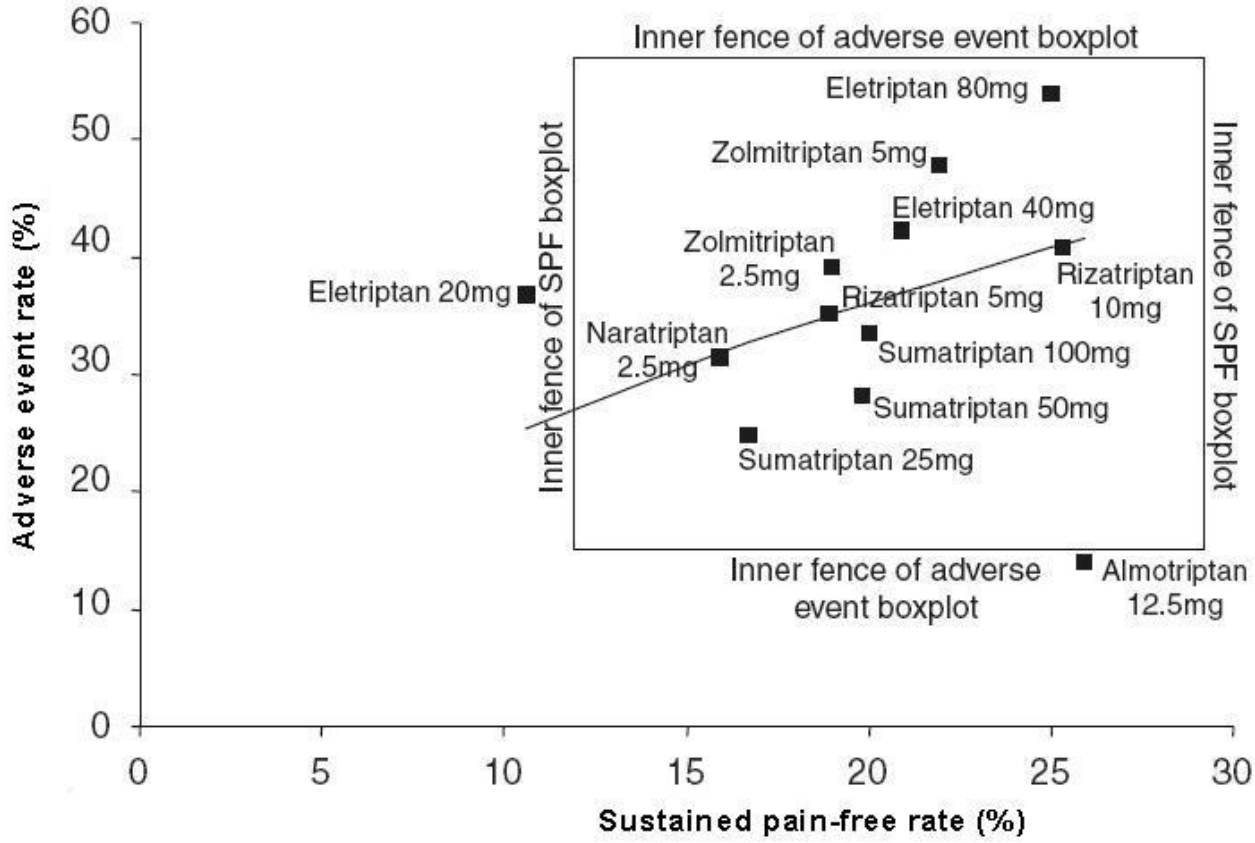

Figure 1 Relationship between the efficacy and adverse events of serotonin 5-$HT_{1B/1D}$ receptor agonists (triptans). Reproduced with permission from Dodick et al. 2007. *CNS Drugs*, 21:73–82. Copyright © 2007 Wolters Kluwer Health.

patients who treated mild pain (66.6%) was nearly twice that recorded in patients who treated moderate or severe pain (36.6%) ($p < 0.001$).

A further retrospective analysis (Dowson et al 2004) evaluated 253 subjects from a cohort of 475 migraineurs who took part in a double-blind, randomized, placebo-controlled trail comparing almotriptan 12.5 mg and sumatriptan 100 mg. The pain-free rates at 2 h were 37.9% for almotriptan 12.5 mg ($p = 0.016$ vs placebo), 35.7% for sumatriptan 100 mg ($p = 0.028$ versus placebo), and 18.9% for placebo. Only almotriptan gave a significantly higher SPF rate (34.7%) than placebo ($p = 0.022$ versus placebo); sumatriptan gave an SPF rate of 29.6%, and placebo one of 17.0%. In a recent multicenter, double-blind, placebo-controlled, parallel-group clinical trial (Mathew et al 2007), 378 migraine patients were randomized to treat three migraine attacks with either almotriptan 12.5 mg or placebo. Patients were instructed to take the study medication within 1 hour of onset of the headache pain. Compared with the placebo group, the 162 patients treated with almotriptan showed significant differences in pain-free (almotriptan 16.7%; placebo 8.4% $p = 0.026$) and pain relief rates (almotriptan 54.3%; placebo 41.1% $p = 0 .019$) within 1 h post dose. Similarly, highly significant differences were found in the almotriptan-treated versus the placebo group in 2-h pain-free (37.0% vs 23.9%, $p = 0.010$), 2-h pain relief (72.3% vs 48.4%, $p < 0.001$) and SPF (24.7% vs 16.1%, $p = 0.040$) rates.

Safety and tolerability

In many studies investigating the AEs typically associated with the triptans, almotriptan was found to show a good safety profile, comparable with that of placebo.

In a pooled analysis (Dodick 2001), three phase 1 dose-finding and pharmacokinetic studies, in healthy subjects, evaluated the safety and tolerability of almotriptan after single doses ranging from 2 to 200 mg. In one of these, single doses of almotriptan, 5 to 200 mg, were administered to 22 healthy subjects, 70% reported an overall of 49 AEs (7 in the placebo group), particularly at the higher doses. The most frequent AEs were headache and drowsiness, also present in the placebo group, while nausea, raised blood pressure, panparesthesia, lightheadedness, heaviness in the chest and muscular fatigue were considered to be related to almotriptan. In another two open-label, single-dose, pharmacokinetic

study, a total of 48 healthy subjects received almotriptan at 12.5 mg and 25 mg. The most common AEs were headache and fatigue, and there were no life-threatening events. A slight, transient (6 h) increase in blood pressure was observed after dosing.

In the same pooled analysis (Dodick 2001), the safety and tolerability of almotriptan was evaluated in phase II and III studies involving about 2500 patients and more than 15000 migraine attacks. In these studies, AEs occurred with an incidence of 3%–5%. The most common symptoms were dizziness, nausea and vomiting, headache, fatigue, paresthesia and drowsiness. Interestingly, the incidence of chest symptoms was only 0.2%. In a phase II trial, almotriptan in doses ranging from 2 to 150 mg was administered to 169 migraineurs: 28 (16.6%) experienced AEs (about 50% in the 150-mg group), 7 of which were probably related to the almotriptan, and there were no serious AEs. In another phase II trial, 139 (18.7%) out of 742 patients reported AEs, of which a significantly greater number were reported in the 25 mg group, the most common being nausea, dry mouth, paresthesia, dizziness and diarrhea. In a phase III, double-blind, placebo-controlled study, 910 patients received a single 6.25 mg or 12.5 mg dose of almotriptan or placebo, while 722 treated three migraine attacks with the study medication. Two hundred and ten patients (23.1%) experienced AEs, without statistically significant differences in incidence emerging between the placebo (21.6%) and the treatment groups (21.1%, 6.25 mg; 25.7%, 12.5 mg). The most frequent AEs, occurring in no more than 3% of patients, included dizziness, vomiting, paresthesia and nausea.

The good tolerability profile of almotriptan has also been confirmed in large clinical studies in which it was compared with sumatriptan.

In a randomized, single-dose, double-blind, parallel-group, placebo-controlled, multicenter clinical study (Dowson et al 2002) that compared almotriptan, 12.5 mg and 25 mg, with sumatriptan 100 mg, a very low rate of AEs was found for both the study drugs. In particular, almotriptan 12.5 mg showed a significantly better AE profile than both placebo (almotriptan = 8.7%, placebo = 6.1%; $p = 0.493$) and sumatriptan (almotriptan 12.5 mg = 8.7%, sumatriptan 100 mg = 22.2%; $p < 0.001$). Conversely, no significant difference was found between the AE profile of almotriptan 25 mg and sumatriptan 100 mg.

In another tolerability study, almotriptan 12.5 mg was compared with sumatriptan 50 mg (Spierings et al 2001). Both drugs showed a good tolerability profile and no serious AEs were reported. The difference in term of treatment-emergent AEs and treatment-related AEs was favorable to almotriptan with an almost significant difference ($p = 0.06$) in the treatment-emergent AEs (15.2% almotriptan, 19.4% sumatriptan) and with high level of significance ($p = 0.001$) in the treatment-related AEs (9.1% almotriptan, 15.5% sumatriptan) with respect to sumatriptan, including the incidence of chest pain (0.3 vs 2.2%, $p = 0.004$).

It is worthy of note that, of all the triptans, almotriptan has been reported to show the lowest incidence of central nervous system (CNS)-related side-effects (Dodick and Martin 2004). The most frequent CNS-related side-effects of the triptans are dizziness and somnolence, and a meta-analysis of 53 studies has shown that almotriptan 12.5 mg (–1.5%) and naratriptan 2.5 mg (1.9%) express them with the lowest incidence (Ferrari et al 2001). Possible explanations could lie in the very low lipophilicity of these compounds and their absence of active metabolites (Dodick and Martin 2004). In a double-blind, randomized clinical trial (Colman et al 2001) evaluating more than one thousand, one hundred migraine patients treated with almotriptan 12.5 mg or sumatriptan 50 mg, the side-effect profile was found to be significantly better ($p = 0.016$) in the almotriptan-treated patients than in the sumatritptan-treated ones.

Almotriptan and the other triptans

Although all the second-generation triptans have been compared head-to-head with sumatriptan, few studies have compared the second-generation triptans with each other, and most comparative conclusions regarding these new agents have been derived from meta-analyses of pooled data. One large meta-analysis of 53 clinical trials of oral triptans used for the acute treatment of migraine, including more than 24,000 patients, showed that almotriptan 12.5 mg, eletriptan 80 mg and rizatriptan 10 mg had the highest likelihood of consistent success, in particular concerning the SPF rates (Ferrari et al 2001). In direct head-to-head trials of almotriptan versus sumatriptan, almotriptan was not superior to sumatriptan on any efficacy end point (Pascual et al 2000; Spierings et al 2001).

More recently, a large, multinational, randomized, double-blind trial including 1298 migraineurs (Goadsby et al 2007) has compared almotriptan 12.5 mg and zolmitriptan 2.5 mg in the treatment of acute migraine. This trial is also the first study to assess the triptans prospectively using SNAE as the primary endpoint, while the secondary endpoints were 2-h pain relief, 2-h pain free, SPF, headache recurrence, and use of rescue medication. The results

showed that there were no differences between almotriptan and zolmitriptan, either in the primary endpoint (SNAE, almotriptan 29.2% vs zolmitriptan 31.8%) or in any of the secondary endpoints. However, compared with zolmitriptan, almotriptan was associated with significantly lower rates of triptan-associated AEs and triptan-associated CNS AEs. Fatigue (2.1% and 4.0% in the almotriptan 12.5 mg and zolmitriptan 2.5-mg groups respectively) and dizziness (1.3% and 2.5%) were among the most common treatment-associated AEs.

In a retrospective analysis (Allais et al 2006) of a trial comparing almotriptan 12.5 mg and zolmitriptan 2.5 mg and involving more than 1000 migraineurs, the efficacy and tolerability profile of these two triptans was compared in a selected sub-population of 255 patients with menstrual migraine. The efficacy endpoints considered were pain relief at 0.5, 1, 1.5 and 2 h; pain-free at 0.5, 1, 1.5 and 2 h; SPF; use of rescue medication within 24 h of drug intake; recurrence within 24 h of treatment; and level of functional impairment before drug intake and after 0.5, 1, 1.5 and 2 h. Almotriptan and zolmitriptan showed similar efficacy and tolerability when used to treat menstrual migraine attacks: 2 h after dosing, 67.9% of almotriptan-treated and 68.6% of zolmitriptan-treated patients had obtained pain relief, whereas 44.9% and 41.2%, respectively, were pain-free. Recurrence rates 2–24 h after dosing were 32.8% for almotriptan and 34.7% for zolmitriptan.

Treatment of acute migraine in adolescents

Despite the high prevalence of migraine in adolescents (about 10%), and its considerable impact on their quality of life (Hamalainen 2006), data on the efficacy of symptomatic treatment of migraine attacks in adolescent patients are too few allow recommendation of the triptans in this age group. In the few studies that have been published on the use of triptans in pediatric patients, nasal sumatriptan and rizatriptan have emerged as effective and safe in children and adolescents respectively (Hershey et al 2001; Winner et al 2002). The efficacy and safety of almotriptan has recently (Charles et al 2006) been investigated in a small group of 15 migraineurs, aged from 11 to 17 years. In all 15 patients, almotriptan (6.25 and 12.5 mg) brought rapid onset of pain relief. There was no re-dosing in $<$24 h in any patient. All the patients were able to continue their normal daily activity during the treatment. No serious AEs were reported; one patient described transient mild stiffness. However, a large population study is necessary to confirm this interesting profile of efficacy and tolerability of almotriptan.

Conclusions

According to the American Academy of Neurology guidelines, the triptans are, on the basis of the significantly better efficacy demonstrated in comparative studies, to be considered the first choice for the treatment of moderate-severe migraine attacks as well as when other treatments fail (Silberstein et al 2000).

The results of controlled clinical trials show almotriptan to be efficacious and well tolerated when used to treat acute migraine attacks. Results from comparative studies and a meta-analysis of 53 randomized, placebo-controlled studies confirm that almotriptan 12.5 mg demonstrates comparable efficacy with sumatriptan 50 and 100 mg. It is worth noting that (at the dose of 12.5 mg) almotriptan emerged as the triptan with the lowest AE rate coupled with the highest SPF rate, and thus with the best SNAE rate. Its rapid onset of effect (in terms of pain relief and pain-free rate), complete the characteristics of this triptan.

This very favorable profile makes almotriptan 12.5 mg one of the first therapeutic options in the treatment of acute migraine attacks, and particularly suitable for early treatment of the attack.

Disclosures

All authors declare that they have no financial or other relationships that might lead to a conflict of interest and that Almirall is not involved in any way in the drafting or writing of this work.

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