

Almotriptan: Review of Efficacy in Treating Migraine in Adolescents

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Abstract: Migraine is a common disabling neurological disorder, often starting in children and adolescents. Triptans, a class of selective 5HT_{1b/d} receptor agonists, have been shown to be effective and well-tolerated as acute therapy in adult migraineurs.

Data examining efficacy and tolerability of triptans in adolescents are limited compared with adults.

Almotriptan has recently been approved by the USA regulatory authorities (FDA) for the acute treatment of migraine headache in adolescent patients (age 12 to 17 years).

A double-blind placebo-controlled, parallel group, multicenter trial demonstrated that oral almotriptan is effective and well tolerated in adolescents, with the 12,5 mg dose associated with the most favourable profile. The aim of this review is to give an overview of clinical data about efficacy and safety of oral Almotriptan in adolescents.

Keywords: almotriptan, 5HT_{1b/d} agonists, adolescence

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Introduction

Migraine is a common neurological disorder, often with an onset in childhood. The estimated prevalence of migraine in the adolescent population ranges from 8% to 28%, according to different studies,^{1–3} with the highest prevalence in older teenagers. Female predominance becomes evident after puberty.

The main clinical characteristics of migraine in children and adolescents differ from those in adults.^{4–6} The duration of the attacks can range between 1 and 48 hours (more frequently between 30 minutes and 2 hours) compared to 4–72 hours in adults, headache is more frequently bilateral (typically frontal-temporal), photophobia or phonophobia do not necessarily occur at the same time, gastrointestinal symptoms are more evident and aura symptoms are less common.

Migraine can significantly affect quality of life in children and adolescents; it can lead to missed school days, impaired school performances, reduced participation in extracurricular activities and social life.^{7–9}

Treatment of pediatric migraine includes acute, preventive and biobehavioural therapy.¹⁰

The goal of acute treatment is a quick response with return to normal activities, without relapse. Adolescent migraineurs have fewer approved acute treatment options than adults.

Ibuprofen at 10 mg/kg and acetaminophen at 15 mg/kg were found to be more effective than placebo in headache relief in children aged 4.0 to 15.8, however, ibuprofen had a better response at two hours and a longer duration of action than acetaminophen.¹¹

In another double-blind, placebo-controlled study, including children aged 6–12 years, ibuprofen suspension at the dose of 7.5 mg/kg was shown to be an effective and well-tolerated agent for pain relief in the acute treatment of childhood migraine, with a decrease of headache pain in 76% of patients compared to placebo at 53%.¹²

The efficacy and safety of other non-steroid anti-inflammatory drugs (NSAIDs) in the treatment of migraine in children and adolescents has not yet been assessed.

Triptans, a class of selective serotonin agonists, have been shown to be effective and well-tolerated as acute therapy in adult migraineurs (ie, triptans may be interchangeable in adults).^{13,14}

Data examining efficacy and tolerability of triptans in adolescents are limited compared with adults, furthermore trials frequently failed to demonstrate statistically significant results largely due to study designs and high placebo response, the latter probably depending on the shorter duration of migraine.

In recent years, several studies have been performed to assess the efficacy and safety of triptans in children and adolescents.

Seven trials studied efficacy and safety of sumatriptan nasal spray in children and adolescents.^{15–22} Five studies were double-blind placebo-controlled trials in which a single attack was treated with sumatriptan nasal spray or placebo.^{15,16,18,20,21} All studies showed that intranasal sumatriptan was generally effective in relieving headache after both 1 and 2 hours, although only four observed a significant difference in relief between sumatriptan and placebo.^{15,16,18,20}

Sumatriptan nasal spray (dose of 10 mg) has been approved in Europe for the treatment of acute migraine with or without aura in adolescents aged 12–17 years.

Preliminary data from an open-label study suggested that zolmitriptan at the doses of 2.5 and 5 mg could be effective and well tolerated in the treatment of migraine in adolescent patients,²³ but a randomized placebo-controlled study failed to demonstrate statistically significant improvement between zolmitriptan and placebo.²⁴

In a double-blind, randomized, placebo-controlled crossover trial zolmitriptan 2.5 was compared to ibuprofen and placebo.²⁵ Oral zolmitriptan 2.5 mg offered significant pain relief and pain freedom versus placebo and showed similar efficacy of ibuprofen, a drug approved for treatment of migraine in children and adolescents.

Promising data on acute migraine therapy in the pediatric population have been obtained with the nasal formulation of zolmitriptan. Zolmitriptan nasal spray was proved to be effective and well tolerated for the acute treatment of migraine in adolescents in a multicenter-randomized double-blind placebo controlled trial.²⁶ This trial used a novel study design to deal with the problem of early placebo responders, in particular each attack was treated initially with placebo within 30 minutes after the headache reached moderate or severe intensity. If a headache response



was achieved at 15 minutes, no additional medication was given. If migraine intensity remained moderate or severe, patients treated the attack with zolmitriptan (5 mg) or placebo according to randomization. Compared with placebo, zolmitriptan produced significant higher rates of symptom relief at 15 minutes, 30 minutes, and 1 hour after the dose.

More limited data concern rizatriptan and eletriptan efficacy and tolerability in infancy and adolescence.

In a single study of eletriptan in adolescents, there was no statistical difference between eletriptan and placebo in pain relief; by contrast there was a significant advantage for eletriptan 40 mg in reducing headache recurrence within 24 hours post-dose.²⁷

Two trials failed to show superiority of rizatriptan 5 mg versus placebo in adolescents over 12 years old,^{28,29} whereas a double-blind, placebo controlled study, including both children and adolescents (age 6 to 17 years) reported effective treatment with oral rizatriptan (5 mg for patients with a body weight of 20 to 39 Kg and 10 mg for those with a body weight of 40 Kg or more).³⁰

A recent double-blind placebo-controlled, parallel group, multicenter trial³¹ demonstrated that oral almotriptan is effective and well tolerated in adolescents, with the 12.5 mg dose associated with the most favourable profile.

Almotriptan has recently been approved by the USA regulatory authorities (FDA) for the acute treatment of migraine headache in adolescent patients (age 12 to 17 years).

Almotriptan is the first oral triptan approved for treatment of migraine in adolescents by the FDA.

The aim of this review is to give an overview of clinical data about efficacy, tolerability and safety of oral almotriptan in adolescents.

Almotriptan: Pharmacological Characteristics, Pharmacokinetics and Clinical Efficacy

Since the first triptan, sumatriptan, was launched in 1991, triptans have been considered efficacious and well-tolerated alternatives to the older anti-migraine drugs, such as ergotamine, and they have become the leading class of prescription medicines in many Western countries.^{13,14,32,33}

Triptans are a class of selective 5-hydroxytryptamine (serotonin; 5-HT) 1b/1d receptor agonists, designed to selectively stimulate the 5-HT_{1b/1d} receptors on both cranial arteries and trigeminal nerves and improve the clinical course of migraine.³⁴

These drugs have mainly three putative mechanisms of anti-migraine action, primarily mediated via 5HT_{1b/1d} receptor agonist activity: cranial vasoconstriction, peripheral neuronal inhibition and inhibition of transmission through second order neurons of the trigeminocervical complex. However relative importance of each of these mechanisms remains uncertain. Seven triptans with five different formulations are currently available for the treatment of acute migraine headache.

Although triptans have a similar mechanism of action, they differ in pharmacological characteristics and pharmacokinetic profiles, such as receptor affinity, bioavailability, and half-life, which may account for their differences in efficacy and tolerability. A meta-analysis of data from 53 trials of oral triptans in adult migraineurs demonstrated that small differences among the agents in this class can be clinically important to individual patients; patients not responding to a single triptan should switch to another triptan.^{13,14}

Almotriptan, a second-generation triptan, exhibits high and specific affinity to 5-HT 1b/1d receptor, 70 times greater than for the 5HT_{1a} receptors and negligible affinity for 5HT₂ and 5HT₄ receptors. Almotriptan is well absorbed orally, with an absolute high bioavailability of approximately 70% (70% versus 14% for sumatriptan). The drug exhibits dose-linear pharmacokinetics and a mean elimination half-life between 3 and 4 h. In humans, approximately 40%–50% of the almotriptan dose is eliminated unchanged in the urine and appears to occur via active tubular secretion of the kidney. The balance of the dose is primarily metabolized, with <5% excreted unchanged in the faeces contribution.^{35–38}

In recent years, a number of randomized controlled trials (RCTs) have been published and clearly documented the efficacy and safety of almotriptan in the treatment of acute migraine in adult age.^{35,39,40}

A meta-analysis of 53 RCTs^{13,14} comparing efficacy, tolerability, and consistency of treatment response for 6 oral triptans against sumatriptan



100 mg in adult age found that almotriptan 12.5 mg was more effective than sumatriptan 100 mg in terms of sustained pain-free rates, and there was no difference in 2-hour headache relief, 2-hour pain-free response, 2–24 hour headache recurrence and adverse events.

Recently a further meta-analysis⁴¹ was conducted to examine efficacy and safety of almotriptan in the adult population. Eight RCTs^{35,39,40,42–46} involving 4995 adult patients were included in the analysis.

The results of this meta-analysis showed that almotriptan 12.5 mg is an effective treatment for an acute migraine attack and its safety profile is similar to placebo in terms of clinically relevant adverse events. A higher dose of almotriptan (25 mg) is also effective in terms of 2-hours headache relief and pain-free response, but it is associated with significantly higher rates of adverse events than placebo.

There were no significant differences in efficacy outcomes comparing almotriptan 12.5 mg against sumatriptan 100 mg and zolmitriptan 2.5 mg, but almotriptan 12.5 mg was associated with significantly fewer adverse events than sumatriptan 100 mg. However, there was no significant difference between almotriptan and sumatriptan in terms of clinically important adverse effects, such as dizziness, somnolence, asthenia, and chest tightness. Almotriptan 12.5 mg was significantly less effective than almotriptan 25 mg for 1-hour pain-free response but associated with significantly fewer patients experiencing adverse events than almotriptan 25 mg. This latter meta-analytic study revealed that almotriptan 12.5 mg is an effective treatment for acute attacks of migraine, in particular, it has been found to be as effective as sumatriptan 100 mg and zolmitriptan 2.5 mg, whereas the risk of adverse events associated with almotriptan 12.5 mg was similar to placebo and significantly lower than sumatriptan 100 mg. Further research is required to assess the comparative efficacy of almotriptan against other triptans.

Recently several studies assessed the opportunity to treat migraine early during the attack and when pain is still mild by means of triptans.

A randomized, double-blind placebo controlled study, showed that treatment with almotriptan within

1 hour of migraine onset, resulted in significantly better clinical outcome than placebo.⁴³

Another trial compared early treatment with almotriptan (ie, within 1 hour) and treatment when headache pain reached moderate or severe intensity. The results showed that early treatment when pain was still mild compared to moderate-severe pain, provided significant benefits in terms of total headache duration, 2-hour pain free, sustained pain free and use of rescue medication.⁴⁷

It was also investigated the effect of early acute migraine intervention with almotriptan versus placebo on functional disability and health-related quality of life (HRQoL) indicators.⁴⁸

Early treatment with almotriptan within 1 hour of migraine pain onset significantly reduced levels of functional disability at 2 and 4 hours post-treatment compared with placebo.

A randomized, multinational, double-blind, placebo-controlled trial^{49,50} was specifically performed to verify almotriptan's response in adult migraine patients taking medication when pain intensity was still mild and within 1 hour of headache onset (mild/early) compared to patients taking drugs when pain became moderate-severe. This trial showed that treatment with almotriptan (12.5 mg) while pain was still mild and within 1 hour of onset, provided statistically significant and clinically relevant enhancement in efficacy compared with late treatment ie, when pain reached higher severity.

Almotriptan Use in Adolescence Pharmacokinetics

Baldwin et al⁵¹ conducted a study to compare pharmacokinetics and tolerability of almotriptan in adolescents and adults.

Plasma and urine drug concentrations were measured to assess the pharmacokinetics of almotriptan in adolescents. Pharmacokinetic evaluation was performed in adolescents to support dose selection for future efficacy studies in this population.

Subjects were healthy male and female adolescents (12–17 years of age) and adults (18–55 years of age), with or without a history of migraine. Thirty-six healthy subjects were enrolled in this study, 18 adolescents and 18 adults. All 36 subjects



completed the study. Although many factors contribute to drug disposition, children of adolescent age are of lower body weight on average than their adult counterpart and thus administering an adult dose to a child may result in higher systemic drug exposure. The study was conducted in order to evaluate this potential outcome and provide guidance on almotriptan dosing in future trials in adolescents. Healthy subjects with or without a history of migraine were allowed to participate since the pharmacokinetics of triptan agents are similar between healthy subjects and subjects with a history of migraine outside of an attack.

Although adolescents were of lower body weight, no statistically significant differences were observed in measures of almotriptan exposure, ie, $AUC_{0-\infty}$ and C_{max} , between the two age groups. The findings were the same when a subgroup of 12–14-year-old children was compared with adults. This observation was not unexpected, since many drugs exhibit a higher systemic clearance in children than in adults, especially when normalized to body weight.

This study showed that almotriptan given as a single 12.5 mg dose was well tolerated in adolescents and there was no need for dose adjustment to treat 12–17 years old patients.

Efficacy and safety

Two trials have been performed to assess efficacy and safety of almotriptan in adolescents.

In a small open-label pilot study 15 patients aged 11–17 years old with a history of migraine with or without aura were treated with almotriptan.⁵² Diagnosis was based on International Headache Society (IHS) criteria. All patients had normal brain imaging studies and no developmental, behavioural or medical problems. Two patients with a body weight <50 Kg received almotriptan at the dose of 6.25 mg, the other patients, who weighed >50 Kg, were given almotriptan 12.5 mg. Reduction in headache severity, disability and adverse effects were studied. In all 15 patients, no serious adverse effects were reported, one patient described transient mild stiffness. In two patients, almotriptan was ineffective; in the remaining 13 patients, almotriptan resulted in rapid onset of pain relief.

All responders were able to continue school and other activities without interruption during almotriptan acute treatment.

In this small pilot study, efficacy, safety and tolerability of almotriptan in adolescents were similar to those of adults.

Subsequently a randomized, double blind, placebo-controlled, multicenter clinical trial was conducted to assess the efficacy and tolerability of oral almotriptan (6.25, 12.5, and 25 mg) versus placebo in a large adolescent migraine population.³¹

Male and female migraineurs aged 12 to 17 years, who would not reach their 18th birthday during the study, were included in the study. Patients were required to have more than 1-year history of migraine with or without aura (according to the International Headache Society criteria) and at least 6-month history of moderate or severe attacks. Inclusion criteria required an attack frequency ranging from 1 to 6 moderate or severe attacks per month during the 2 months before the enrolment, attacks lasting >4 hours without treatment, and attacks occurring at intervals >24 hours.

Eligible patients, after a preliminary clinical visit, were randomized 1:1:1:1 within 2 age groups (12 to 14 years and 15 to 17), with patients receiving 1 dose of study medication (almotriptan 6.25, 12.5, 25 mg or placebo). During the treatment period, patients were instructed to take the study medication to treat their first migraine attack as soon as possible and no more than 4 hours after the onset of moderate-severe pain. Patients performed the final study visit 2 to 14 days after the migraine attack treated with study medication.

The primary efficacy endpoint was headache pain relief 2 hours after dosing (decrease from moderate or severe pain intensity to mild or no pain) and absence of nausea, photophobia, and phonophobia 2 hours after dosing as coprimary endpoints. Secondary efficacy endpoints included headache relief, presence of associated symptoms and freedom from headache at 0.25, 0.5, 1.0 and 1.5 hours after dosing, headache recurrence 2 to 24 hours after dosing in patients who achieved 2 hours pain relief, time to headache recurrence, use of rescue medication, sustained pain relief, sustained pain-free, safety and tolerability were also assessed.



866 patients were enrolled and randomized by 93 investigators in the United States, Argentina, Colombia and Mexico. Data from 720 patients were analyzed for safety and tolerability and data from 714 patients were analyzed for efficacy.

The 2-hour pain-relief rate, adjusted for baseline severity, was significantly greater for patients receiving almotriptan 25 mg compared with those receiving placebo (66,7% versus 55,3%), but there were not significant differences in the incidence of nausea, photophobia and phonophobia at 2 hours.

The 2 hour pain relief rates, not adjusted for baseline severity, were significantly higher with almotriptan 6.25 mg (71,8%), 12.5 mg (72,9%), and 25 mg (66,7%) than with placebo (55,3%).

Rates for sustained pain relief between 2 and 24 hours were also significantly greater with almotriptan 6.25 mg (67,2%), 12.5 mg (66,9%), and 25 mg (64,5%) than with placebo (52,4%).

With regard to neurovegetative symptoms at 2 hours post-dose almotriptan 12,5 mg showed statistically significant decrease of photophobia and phonophobia, but not of nausea.

A subanalysis was conducted according to age group respectively (12 to 14 or 15 to 17).

Two hour pain-relief was significantly greater than placebo with all the 3 doses of almotriptan in patients aged 15 to 17 years, whereas the 2 hour pain relief rates for patients aged 12 to 14 years was not significantly different from placebo. The subanalysis adjusted for baseline headache severity showed similar results.

Age group subanalysis on the presence of associated symptoms showed a significantly lower incidence of photophobia and phonophobia at 2 hours with almotriptan 12.5 mg compared with placebo for patients aged 15 to 17 years and a significantly lower incidence of photophobia with almotriptan 12.5 mg compared with placebo for those aged 12 to 14 years. The data from the present study showing that the older adolescents responded to almotriptan better than younger adolescents suggest that a certain level of migraine “maturation” may be necessary for triptan response.

Almotriptan treatment was well tolerated, with the most common adverse events (>2%) of nausea, dizziness, and somnolence.

Placebo response rates were similar to those seen in other trials of oral triptans in adolescents, suggesting that the significant effect of almotriptan on pain relief is not due to a lower placebo response rate.

Conclusions

Children and adolescents have fewer approved symptomatic drugs than adults. As analgesic drugs, ibuprofen and acetaminophen have been shown to be effective and safe to treat migraine attacks in the pediatric population. Data examining efficacy and tolerability of triptans in children and adolescents are limited compared with adults and trials frequently failed to demonstrate statistically significant results largely due to high placebo response. Sumatriptan nasal spray (dose of 10 mg) has been approved in Europe for the treatment of acute migraine with or without aura in adolescents aged 12–17 years old.

Oral almotriptan was recently shown efficacious for relieving migraine headache pain in adolescents, with the 12.5 mg dose associated with the most favorable efficacy profile with respect to treat headache pain and associated symptoms of migraine (photophobia and phonophobia) in a large controlled study.

Almotriptan is the first oral triptan to be approved by the American FDA for the acute treatment of migraine in adolescent patients, aged 12 to 17 years old.

The availability of an efficacious oral triptan in adolescents might provide a significant contribution to the treatment strategy in this young migraine population and, to a greater extent, offer the opportunity of a decrease in their disability and an improvement in their quality of life.

Future trials are needed to assess the efficacy and safety of other symptomatic options in children and adolescents and trials should be performed with novel study design in order to overcome the high placebo response in the pediatric population.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.



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