

Drug Class Review on Triptans



Update #5: Preliminary Scan Report

April 2010

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:

Update #4 Final Report was completed in June 2009.

Scope and Key Questions

Key Questions

1. How do effectiveness and efficacy outcomes (reduced severity and duration of symptoms, functional outcomes, quality of life, etc) differ for adult patients with migraine within the following treatment comparisons:
 - 1a. Monotherapy compared with monotherapy
 - 1b. Fixed-dose tablets containing a triptan compared with triptan monotherapy
 - 1c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

2. How do the incidence and nature of adverse effects (serious or life-threatening or those that may adversely effect compliance) differ for adult patients with migraine within the following triptan treatment comparisons:
 - 2a. Monotherapy compared with monotherapy
 - 2b. Fixed-dose tablets containing a triptan compared with triptan monotherapy
 - 2c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

3. Are there subgroups of patients based on demographics, other medications, or comorbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

Adult patients with any level of migraine (mild, moderate, severe), with or without aura. Definition of migraine must be explicit, to exclude other types of headache (for example, tension headache).

Interventions (oral, nasal, and injectable)

Almotriptan (Axert [®])
Eletriptan (Relpax [®])
Frovatriptan (Frova [®])
Naratriptan (Amerge [®])
Rizatriptan (Maxalt [®])
Rizatriptan orally disintegrating tablet (Maxalt-MLT ^{®a} , Maxalt RPD ^b)
Sumatriptan oral tablet, nasal spray, subcutaneous injection (Imitrex ^{®a} , Imitrex DF ^b , Imitrex StatDose [®] , Imitrex PD ^b)
Sumatriptan-naproxen sodium fixed-dose combination product (Treximet [®]) ^a
Zolmitriptan oral tablet, nasal spray (Zomig [®] , Zomig Nasal Spray ^b)
Zolmitriptan orally disintegrating tablet (Zomig-ZMT [®] , Zomig Rapimelt ^b)

^a Not available in Canada.

^b Canadian product. Not available in the United States.

Effectiveness/efficacy outcomes

- Reduction or resolution of symptoms (pain, nausea, vomiting, photophobia, phonophobia), reduction of duration of symptoms, duration of improvement, consistency of effectiveness (proportion of headaches successfully treated per patient), functional outcome (for example, change in days of work lost), quality of life, or adverse effect (including drug interactions).
- Measures: Response, time to response, pain-free, sustained response, sustained pain-free, rescue (use of rescue medications), recurrence (reappearance of any degree of symptoms within 24 or 48 hours) after response or becoming pain-free, time to relief, relief of associated symptoms, tablets per attack, and patient satisfaction.

Harms

- Overall withdrawals
- Withdrawals due to any adverse events
- Withdrawals due to specific adverse events (central nervous system effects, chest tightness)

Study designs

- For effectiveness/efficacy, study is a controlled clinical trial in an outpatient setting or a good-quality systematic review.
- For harms, the study is a controlled clinical trial or observational study.

METHODS

New Drug Information Search

To identify information on new drugs, new indications and new safety alerts, we searched the websites of FDA's Center for Drug Evaluation and Research (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>) and MedWatch websites (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (<http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/index-eng.php>).

Literature Search

To identify relevant citations, we searched MEDLINE (January 2009 to April 2010). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X2).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

None

New Indications

Almotriptan: Acute treatment of migraine in adolescents, aged 12 to 17 years - 5/2009

New Safety Alerts

The only new safety information identified included changes to the Warnings and Precautions section of the product labels for almotriptan and frovatriptan. In March of 2009, information concerning the risk of serotonin syndrome with concomitant use of SSRIs/SNRIs was added for both almotriptan and frovatriptan. Additionally for almotriptan, in April of 2009, advice was added that, due to its chemical structure containing a sulfonyl group, caution should be used in prescribing almotriptan to patients with known hypersensitivity to sulfonamides.

New Studies

We identified 30 potentially relevant citations. Of those, there are 5 new potentially relevant controlled clinical trials (Appendix A), including one head-to-head trial that compared almotriptan and rizatriptan (Ng-Mak 2009) and 4 placebo-controlled and active-control trials.

APPENDIX A

Cady, R. K., V. T. Martin, et al. (2009). "Rizatriptan 10-mg ODT for early treatment of migraine and impact of migraine education on treatment response." Headache **49**(5): 687-96.

OBJECTIVE: To examine the efficacy of rizatriptan 10-mg orally disintegrating tablet (ODT) for treating migraines of mild intensity soon after onset, with or without patient-specific migraine education. **BACKGROUND:** Studies have shown rizatriptan tablet efficacy in early migraine treatment. **METHODS:** In this randomized, placebo-controlled, double-blind, factorial design study, adults with a history of migraine were assigned to rizatriptan 10-mg ODT patient education (personalized summary of early migraine signs and symptoms) or placebo patient education in a 1 : 1 : 1 : 1 ratio. Patients were instructed to treat 1 attack at the earliest time they knew that their headache was a migraine, while pain was mild. During the next 24 hours, patients assessed pain severity, associated symptoms, functional disability, use of rescue medication, and treatment satisfaction. The primary endpoint was pain freedom at 2 hours; a key secondary endpoint was 24-hour sustained pain freedom. **RESULTS:** Of 207 patients randomized to treatment, 188 (91%) treated a study migraine. Significantly more patients taking rizatriptan reported pain freedom at 2 hours compared with placebo (66.3% vs 28.1%, $P < .001$). Similarly, significantly more patients taking rizatriptan reported 24-hour sustained pain freedom (52.2% vs 17.7%, $P < .001$). A greater proportion of patients in the rizatriptan + education group reported pain freedom at 2 hours compared with those in the rizatriptan + no education group (71.7% vs 60.9%, $P = .430$). Few adverse events were reported. **CONCLUSION:** Rizatriptan 10-mg ODT, when taken early, while headache pain is mild, was superior to placebo at providing pain freedom at 2 hours and 24-hour sustained pain freedom.

Mathew, N. T., S. Landy, et al. (2009). "Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life." Headache **49**(7): 971-82.

OBJECTIVE: To evaluate efficacy and tolerability of a single, fixed-dose tablet of sumatriptan 85 mg/naproxen sodium 500 mg (sumatriptan/naproxen sodium) vs placebo in migraineurs who had discontinued treatment with a short-acting triptan because of poor response or intolerance. **BACKGROUND:** Triptan monotherapy is ineffective or poorly tolerated in 1 of 3 migraineurs and in 2 of 5 migraine attacks. In April, 2008, the Food and Drug Administration approved the combination therapy sumatriptan/naproxen sodium, developed specifically to target multiple migraine mechanisms. This combination product offers an alternative migraine therapy for patients who have reported poor response or intolerance to short-acting triptans. **METHODS:** Two replicate, randomized, multicenter, double-blind, placebo-controlled, 2-attack crossover trials evaluated migraineurs who had discontinued a short-acting triptan in the past year because of poor response or intolerance. Patients were instructed to treat within 1 hour and while pain was mild. **RESULTS:** Patients ($n = 144$ study 1; $n = 139$ study 2) had discontinued an average of 3.3 triptans before study entry. Sumatriptan/naproxen sodium was superior ($P < .001$) to placebo for 2- through 24-hour

sustained pain-free response (primary end point) (study 1, 26% vs 8%; study 2, 31% vs 8%) and pain-free response 2 hours post dose (key secondary end point) (study 1, 40% vs 17%; study 2, 44% vs 14%). A similar pattern of results was observed for other end points that evaluated acute (2- or 4-hour), intermediate (8-hour), or 2- through 24-hour sustained response for migraine (ie, pain and associated symptoms), photophobia, phonophobia, or nausea (with the exception of nausea 2 and 4 hours post dose). The percentage of patients with at least 1 adverse event (regardless of causality) was 11% with sumatriptan/naproxen sodium compared with 4% with placebo in study 1 and 9% with sumatriptan/naproxen sodium compared with 5% with placebo in study 2. Only 1 adverse event in 1 study was reported in $\geq 2\%$ of patients after treatment with sumatriptan/naproxen sodium and reported more frequently with sumatriptan/naproxen than placebo: chest discomfort was reported in 2% of subjects in study 1, and no events met this threshold in study 2. No serious adverse events attributed to study medication were reported in either study. CONCLUSION: In migraineurs who reported poor response to a short-acting triptan, sumatriptan/naproxen sodium was generally well tolerated and significantly more effective than placebo in conferring initial, intermediate, and sustained efficacy for pain and migraine-associated symptoms of photophobia and phonophobia.

Merelle, S. Y. M., E. G. M. Couturier, et al. (2009). "Large-scale screening and subsequent effects of migraine treatment on the work floor in the Netherlands." *Cephalalgia* **29**(6): 606-15.

In a large retail business group the ID Migraine Screening Test was sent to employees with three or more absences from work in the past year ($n = 2893$). Employees with positive results were invited for a neurological consultation and migraine patients were randomly assigned to: first attack 'treated as usual' and the second attack treated with 40 mg eletriptan, or reversed order. Of the 2893 employees, 799 responded (28%), 260 were positively screened for migraine (33%), 84 patients were diagnosed by a neurologist and 41 of the 75 included patients completed the protocol. Eletriptan induced pain-free response in 33.3% of the patients at 4 h compared with 0% after 'non-specific' treatment ($P = 0.03$). Eletriptan also significantly improved quality of life, but differences in absence from work and productivity loss could not be detected. In conclusion, in-company screening can be beneficial for undertreated employees, but implementation obstacles can reduce the effectiveness of screening.

Ng-Mak, D. S., X. H. Hu, et al. (2009). "Migraine treatment with rizatriptan and almotriptan: a crossover study." *Headache* **49**(5): 655-62.

BACKGROUND: Rizatriptan and almotriptan are effective and well-tolerated triptans that have not been compared directly. OBJECTIVE: To evaluate the effectiveness of rizatriptan 10 mg and almotriptan for the acute treatment of migraine, in a real-world setting. METHODS: Of a large, multicenter, open-label, crossover study, we conducted a substudy to contrast the effectiveness of rizatriptan 10 mg and almotriptan 12.5 mg for the acute treatment of 2 migraine attacks in a sequential, crossover manner. Time to outcome was assessed using stopwatches. Mean and median times to onset of pain relief (PR) and pain freedom (PF) for rizatriptan and almotriptan were compared. The

effect of rizatriptan on times to onset of PR and PF, adjusting for potential confounding factors (treatment sequence, treatment order, and use of rescue medication), was computed via a Cox proportional hazard model. RESULTS: Out of the 146 patients taking almotriptan as their usual care medication, 79 used stopwatch for both attacks. Significantly more patients taking rizatriptan achieved onset of PR within 2 hours after dosing than those taking almotriptan (88.6% vs 73.4%, $P = .007$). A higher proportion of patients taking rizatriptan achieved PF within 2 hours after dosing than those taking almotriptan (55.7% vs 45.6%, $P = .10$). Times to onset of PR and PF were significantly shorter with those patients taking rizatriptan than with those taking almotriptan (median time to PR: 45 vs 60 minutes, $P = .002$; median time to PF: 100 vs 135 minutes, $P = .004$). The adjusted proportional hazard ratios (rizatriptan vs almotriptan) for times to onset of PR and PF were 1.51 (95% confidence interval 1.20 to 1.88) and 1.42 (95% confidence interval 1.15 to 1.76), respectively. More patients were very satisfied when treating their attacks with rizatriptan than with almotriptan. Rizatriptan was preferred by most patients. CONCLUSIONS: Times to achieve PR and PF were significantly shorter for patients using rizatriptan, as compared with those using almotriptan.

Spierings, E. L. H. and C. Keywood (2009). "Rapid responders to frovatriptan in acute migraine treatment: results from a long-term, open-label study." *Pain Medicine* **10**(4): 633-8.

BACKGROUND: The chronic nature of migraine and the reliance on acute treatment constitute the basis of the present long-term, open-label study. OBJECTIVES: First, assessment of the tolerability and safety of frovatriptan, 2.5-7.5 mg taken orally over 24 hours, for the acute treatment of migraine, repeatedly over a 12-month period. Second, assessment of the efficacy and tolerability of a second, double-blind dose of 2.5-mg frovatriptan, compared with placebo, for nonresponse at 2 hours after treatment of moderate or severe headache with 2.5-mg frovatriptan. RESULTS: With regard to the first attack treated, 173 (36%) of the 486 subjects in the study did not take a second dose at 2 hours for nonresponse. At 2 hours and 4 hours, these "rapid responders" experienced a decrease in headache intensity from moderate or severe to mild or no pain in 84% and 98%, respectively ("headache response"). Six percent of them experienced recurrence of moderate or severe headache within 24 hours following a response at 4 hours and 12% took rescue medication. The response, measured in terms of median time to "complete migraine relief," was maintained over 30 subsequent migraine attacks, treated from attack 2 onwards over the course of 12 months. CONCLUSION: Frovatriptan provides a remarkably fast and high headache response in a subgroup of more than one-third of migraineurs, with a very low 24-hour headache recurrence and low rescue medication intake.