

Oral Zolmitriptan is Effective as Early as 30 Minutes in the Treatment of Migraine Associated with Menses: Results of a Large Multicenter Placebo-Controlled Study

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Conclusions

Zolmitriptan was shown to have an onset of action as early as 30 minutes in this population of women treating migraine associated with menses.

Secondary endpoints demonstrate that zolmitriptan is more effective than placebo in achieving a pain-free state, and reducing pain intensity as measured by the proportion of patients who had a 50% or greater on VAS pain index score, and the proportion of patients who demonstrated a 30 mm drop in VAS pain index score.

Zolmitriptan was effective in treating younger (18 to 39 years) and older women (ages 40 to 55), with older women demonstrating a slightly higher efficacy response. The reason for this requires further study.

Data collected for 3 months following conclusion of the study showed that these prospective data were consistent with the demographic data collected during the pretreatment period. Most of the women included in this study migraine associated predominantly with menses.

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References

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Introduction

This study prospectively investigates the efficacy of zolmitriptan in migraine associated with menses. Retrospective data from previous prospective zolmitriptan trials suggests that the drug is effective in the treatment of migraine associated with the menstrual cycle, but prospective studies are lacking. Additionally, this study specifically characterizes the population of women studied by enrolling participants in a 3-month follow-up period to track the time and frequency of migraine attacks and the relationship to menses.

Methods

Study Objectives

To evaluate the safety and efficacy of oral zolmitriptan (versus placebo) for the treatment of menstrual-associated migraine headaches.

Study Design

- Multicenter, double-blind, randomized, parallel-group, placebo-controlled 3-attack study
- Patients were recruited from 18 participating centers in the United States and Canada
- Patients were randomized to one of two treatment groups: zolmitriptan or placebo
- Patients participated in a 3-month follow-up where the frequency of migraine attacks and menstrual periods were recorded on daily diaries
- Treatment was intensity based:
 - Mild attacks: zolmitriptan 1.25 mg tablet (one half of a zolmitriptan 2.5 mg tablet)
 - Moderate attacks: zolmitriptan 2.5 mg tablet
 - Severe attacks: zolmitriptan 5 mg

Patient Population

- Women aged 18 years to 55 years with a history of predictable menstrual-associated migraine headaches and regular menstrual periods.
- Establish diagnosis of menstrual migraine headache (modified from the Headache Classification Committee of the International Headache Society, 1988).
- Migraine headaches qualifying for treatment occurred within 72 hours before onset of menses through 5 days after the start of menstrual flow.
- Patients had at least 2 menstrual-associated migraine headaches of moderate or severe intensity within the last 3 preceding months.

Rescue and Concomitant Medications

- Escape (rescue) medications were permitted 2 hours after initial treatment, and included: NSAIDs, analgesics, or sedatives.
- Sumatriptan, naratriptan, rizatriptan, and ergotamines were not permitted within 24 hours after taking the last dose of study medication.
- Use of prescription zolmitriptan as an escape medicine was permitted. However, combination dosages of zolmitriptan study medication and zolmitriptan prescription medication could not exceed 15 mg within a 24-hour period.
- Use of prophylactic medications was permitted during the study if their use had been stable for at least 2 months before randomization.

Results

Demographics

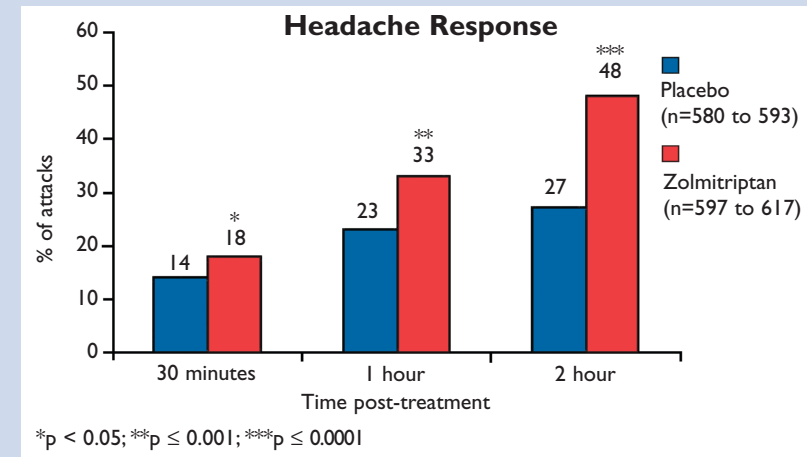
A total of 579 women with a history of migraine associated with menses were enrolled in the study; 287 were randomized to zolmitriptan and 292 were randomized to placebo. Of those randomized, 510 participants took study medication and defined the intent-to-treat population (ITT) and safety population: 260 in the zolmitriptan group and 250 in the placebo group. Overall, 614 attacks were treated in the zolmitriptan treatment group and 585 attacks in the placebo treatment group. Demographic characteristics were similar between the two treatment groups.

Baseline Headache Intensity

The overall percentage of zolmitriptan subjects reporting treatment of mild, moderate, and severe attacks was similar between the two treatment groups, with a slightly higher prevalence of severe attacks in the zolmitriptan-treatment group.

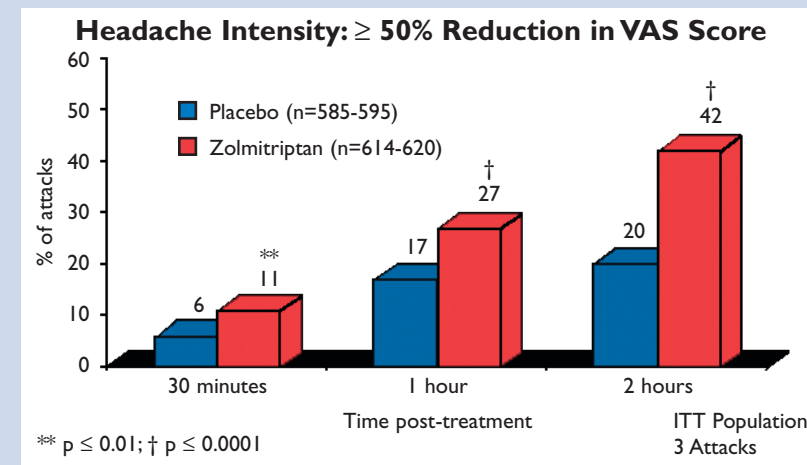
- Zolmitriptan: mild 17%, moderate 57%, and severe 26%.
- Placebo: mild 17%, moderate 61%, and severe 22%.

Efficacy

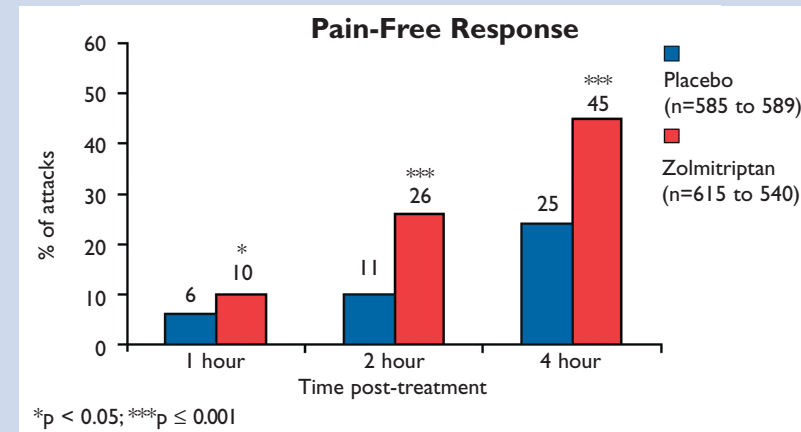


The primary endpoint of this study was 2-hour headache response (defined as a decrease in moderate to severe pain to mild or no pain, or a decrease in mild migraine to no pain), which showed statistically significant improvement over placebo. Efficacy was seen as early as 30 minutes following treatment. Patients treated between one and three attacks; data analyzed on ITT population.

Treatment groups were split into two subgroups and efficacy response was evaluated according to age group. Women ages 40 to 55 had a higher clinical response to zolmitriptan treatment compared to the younger age group (18 to 39 years). Patients treated between one and three attacks; data analyzed on ITT population.



The percent of attacks achieving a 50% reduction or greater in VAS over baseline measures was 42% in women treated with zolmitriptan compared to 20% in the placebo group (odds ratio 2.89, CI 2.14, 3.91; p<0.0001). The percent of attacks showing a 30-point drop in VAS scores also favored zolmitriptan (35%) vs. placebo (13%) (odds ratio 3.45, CI 2.47, 4.81; p<0.0001). Patients treated between one and three attacks; data analyzed on ITT population.



The percent of attacks achieving a pain-free endpoint was statistically significantly larger for patients treated with zolmitriptan than for those treated with placebo. At 1 hour, 10% of attacks achieved a pain-free response, compared to 6% of those treated with placebo (odds ratio 1.76, CI 1.06, 2.94; p=0.0403). Similarly, more attacks achieved a pain-free state at 2 hours (26% vs. 10%, respectively) and 4 hours (45% vs. 24%) following treatment: (2 hours—odds ratio 3.08, CI 2.10, 4.52, P<0.0001; 4 hours—odds ratio 2.62, CI 1.88, 3.65, p<0.0001). Patients treated between one and three attacks; data analyzed on ITT population.

Tolerability

- Overall, 72 subjects (28%) in the zolmitriptan treatment group and 57 (23%) in the placebo group had at least one adverse event.
- Of the adverse events considered treatment-related; 41 occurred in subjects in the zolmitriptan group and 23 occurred in subjects receiving placebo.
- Serious adverse events were recorded for 3 subjects in the zolmitriptan treatment group: accidental injury, convulsion, and bronchitis. These were considered to be unrelated to treatment. Two subjects in the placebo-treatment group reported serious adverse events, intracranial pressure and accidental injury.

Women ages 18 to 39 had a larger incidence of AEs, compared to the older women. This increase in AEs was most evident with zolmitriptan treatment, with minor increases also observed in the placebo-treated women ages 18 to 39 years.

3-Month Patient Follow-up

Overall, 179 women in the zolmitriptan treatment group and 183 in the placebo group provided migraine demographic data for 3 months following the termination of the treatment period. The incidence of migraine occurring in association to menses, compared to nonmenstrual periods, was similar across both treatment groups.

- 71% of women in the zolmitriptan group and placebo reported having a migraine attack outside of the menstrual window.
- The mean number of nonmenstrual headaches during the treatment period was 4 attacks during the 3-month treatment period (averaging 1.3 attacks per month), compared to an average of 3 nonmenstrual migraine attacks in the placebo group (1 attack per month).
- During the 3-month follow-up period, the mean number of menstrual migraine attacks increased slightly to 5 attacks in both the zolmitriptan-treatment group and placebo-treatment group (averaging 1.67 attack per month).
- The percent of women who experienced migraine associated with menses in 2 out of 3 attacks (as required for study inclusion) was 91% in the zolmitriptan-treatment group and 90% in the placebo group, supporting a study recruitment population who claimed to have migraine associated with their menstrual cycle.
- During the follow-up period, the overall percentage of zolmitriptan subjects reporting mild, moderate, and severe attacks was 11%, 55%, and 34%, respectively. The percent of mild, moderate and severe attacks in the placebo-treatment group was 12%, 54%, and 34%, respectively.

Demographic Characteristics of the Two Treatment Groups			
Demographic Characteristics		Zolmitriptan	Placebo
Age (y) at entry:	Mean	37.2	37.9
	SD	7.4	4.2
	Range (y)	18 to 55	19 to 51
Age distribution:	18 to 39 yr	148 (57%)	133 (53%)
	40-55 yr	112 (43%)	117 (47%)
Mean age at onset		21	20
Mean number of attacks per month		3	3
Average number of days a month with nonmigraine headache		3	3
Duration of untreated attack:	0 to 12 hrs	100 (39%)	111 (44%)
	> 12 to 24 hrs	65 (25%)	29 (12%)
	> 24 to 48 hrs	50 (19%)	49 (20%)
	> 48 to 72 hrs	34 (13%)	43 (17%)
	> 72 hrs	11 (4%)	18 (7%)

Efficacy Response Measures (ITT Population)						
Variable	Zolmitriptan response rate (attacks treated)	Placebo response rate	Odds ratio	95% CI	P value	
4-point scale						
	30 minutes	18% (112/617)	14% (85/593)	1.50	1.04, 2.17	0.0307
	1 hour	33% (201/613)	23% (135/585)	1.83	1.33, 2.50	0.0002
2 hours	48% (288/605)	27% (154/580)	2.80	2.09, 3.75	<0.0001	
2-hour IHS headache response (excludes mild patients)	50% (256/509)	27% (133/487)	3.01	2.19, 4.14	<0.0001	
2-hour 50% drop in VAS from baseline	42% (259/614)	20% (119/585)	2.89	2.14, 3.91	<0.0001	
2-hour 30 mm drop in VAS score from baseline	35% (209/597)	13% (77/580)	3.45	2.47, 4.81	<0.0001	

Adverse Events ≥1% Incidence Considered Treatment Related			
Adverse Event	Zolmitriptan (n=260)	Placebo (n=251)	
WHOLE BODY			
	Asthenia	18 (7%)	7 (3%)
	Tightness	4 (2%)	1 (1%)
		7 (3%)	5 (2%)
DIGESTIVE			
		8 (3%)	9 (4%)
	Gastritis	1 (1%)	3 (1%)
	Nausea	4 (2%)	5 (2%)
NERVOUS SYSTEM			
		23 (9%)	14 (6%)
	Dizziness	8 (3%)	4 (2%)
	Paresthesia	10 (4%)	4 (2%)
	Somnolence	9 (3%)	5 (2%)
RESPIRATORY SYSTEM			
		6 (2%)	0
		3 (1%)	0