
Brief Communication

Frovatriptan for Prophylactic Treatment of Cluster Headache: Lessons for Future Trial Design

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Objective.—The aim of this study was to determine whether frovatriptan would show efficacy in short term prophylactic treatment of episodic cluster headache (ECH) in comparison to placebo.

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Background.—The 5-hydroxytryptamine_{1B/D} (5-HT_{1B/D})-agonists naratriptan, eletriptan, and frovatriptan have been shown to reduce the frequency of ECH. So far, no double-blind placebo-controlled trials have investigated the potential prophylactic effects of 5-HT_{1B/D}-agonists in ECH.

Methods.—The trial was conducted as a multi-center, placebo-controlled, randomized, double-blind, prospective phase III parallel-group trial with two independent treatment groups (5 mg frovatriptan vs placebo). It was planned to randomize about 96 patients (48 patients per group) into the trial to obtain 80 evaluable patients (40 patients per group).

Results.—The study was prematurely discontinued after 13 months and enrollment of 11, instead of the planned 80 patients, by the sponsor due to infeasibility. Recruitment was slow and each of the patients included conducted major protocol violations. The differences in the primary and secondary endpoints were not significant.

Conclusion.—This study shows that particular therapeutic aims are impossible to be addressed in a double-blind, randomized, parallel group, study design with specific inclusion and exclusion criteria according to the International Headache Society (IHS) guidelines for controlled trials of drugs in cluster headache. Further studies are required to evaluate the potential efficacy of triptans in the prophylactic treatment of ECH. The outcome of the trial suggests that the recommendations of the Guidelines for controlled Trials of Drugs in Cluster Headache from the IHS should be revised.

Key words: cluster headache, frovatriptan, trial design, prophylactic treatment, guidelines

Abbreviations: AE adverse event, ECH episodic cluster headache, IHS International Headache Society

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Inhalation of oxygen, the 5-hydroxytryptamine_{1B/D}-agonists (5-HT_{1B/D}-agonists) sumatriptan sc and zolmitriptan nasal spray are effective in the acute treatment of episodic cluster headache (ECH).¹⁻⁴ For the prophylactic treatment of cluster headache verapamil is considered to have the best balance of efficacy and tolerability.^{5,6} The evidence for the effectiveness of lithium is poor.^{7,8} The efficacy of oral 5-HT_{1B/D}-agonists in prophylactic treatment of ECH was investigated only in open trials with few patients. In these trials naratriptan,⁹ eletriptan,¹⁰ and frovatriptan¹¹ have been shown to reduce the frequency of ECH. Interestingly, sumatriptan was not effective.¹² So far, no double-blind placebo-controlled trials investigating the prophylactic effects of 5-HT_{1B/D}-agonists in ECH are available.

The 5-HT_{1B/D}-agonist frovatriptan is the triptan with the longest half-life (26 hours) and the strongest affinity to 5-HT_{1B}- and 5-HT_{1D}-receptors.¹³ In Germany, frovatriptan succinate is approved for the acute treatment of migraine attacks with a dosage of 2.5 mg. Safety studies, however, encompassed single dosages up to 100 mg per attack (Vernales, data on file).

The aim of this study was to determine whether frovatriptan would show efficacy in short term prophylactic treatment of ECH in comparison to placebo.

METHODS

Ethical and Legal Aspects.—The clinical trial protocol was approved by the independent ethics committee of the University of Essen, Germany, and by the regulatory health authorities in Germany (BfArM). The study is registered under the EudraCT Number 2004-004999-361 at the European Medicines Agency (EMA).

Clinical Trial Objectives.—The primary endpoint was the reduction of mean cluster headache attack frequency during the 2-week treatment period. Secondary endpoints were mean cluster headache attack frequency per week during the first and second week of the treatment period and the 1-week follow-up period, mean pain intensity and the total duration of cluster headache attacks, presence or absence of associated autonomic symptoms, frequency of oxygen use for symptomatic treatment and use of additional drug treatment, quality of life documented in the SF-36 questionnaire, global evaluation of therapy and therapy satisfaction.

Trial Design.—The trial was conducted as a multi-center (6 centers), placebo-controlled, randomized, double-blind, prospective phase III parallel-group trial with 2 independent treatment groups (5 mg frovatriptan vs placebo). Consecutive patients should be recruited from the headache outpatient centers of 6 supraregional specialized headache clinics.

The trial was designed according to the recommendations of the Guidelines for controlled Trials of Drugs in Cluster Headache from the International Headache Society.¹⁴ The trial consisted of a run-in period (4 to 7 days), a treatment period (14 days), and a follow-up period (7 days). It was planned to randomize about 96 patients (48 patients per group) into the trial to obtain 80 evaluable patients (40 patients per group). The sample-size calculation was based on preliminary data from Siow et al.¹¹ They described cluster headache frequencies at baseline and after treatment with frovatriptan for 12 patients. Mean and standard deviation at baseline were about 2.8 and 1.03 and after treatment about 1.08 and 1.36 for cluster headache frequency per day.

Statistical Methods.—All efficacy analyses were done by intention-to-treat, which included all patients who had taken study medication and had at least one measurement of the primary variable during run-in and one during the treatment-period available.

For the primary variable treatment groups were compared using the 2-sided exact Wilcoxon-Mann-Whitney tests at a significance level of 5%. Secondary efficacy variables and safety were analyzed by descriptive methods, only.

Inclusion and Exclusion Criteria.—Inclusion criteria: Written informed consent, age between 18 and 65 years, suffering from ECH according to the criteria of the IHS¹⁶:

- Patient suffers at least from a second phase of cluster headache
- Duration since onset of current episode at least 1 week
- Expected duration at least 6 weeks after start of screening
- Demonstrated response to oxygen inhalation (defined as relevant change in headache severity).
- Attack frequency between 1 attack every other day and 8 attacks per day at visit 2.

The most important exclusion criteria were change of concomitant prophylactic medication one month prior to visit 1, concomitant prophylactic

Table 1.—Protocol Violations (SAF, n = 11)

	Number (%) of Patients				
	Frovatriptan (n = 5)		Placebo (n = 6)		Total (n = 11)
Violation of in/exclusion criteria	5	(100.0)	3	(50.0)	8 (72.7)
Intake of prohibited medication	4	(80.0)	2	(33.3)	6 (54.6)
Lost to follow up	1	(20.0)	—		1 (9.1)
Violation of time window for visits	2	(40.0)	1	(16.7)	3 (27.3)
Informed consent signed at visit 1	—		1	(16.7)	1 (9.1)
Non- or missing compliance	1	(20.0)	2	(33.3)	3 (27.3)
Missing documentation	1	(20.0)	—		1 (9.1)
Total number of patients with deviations	5	(20.0)	6		11
Total number of deviations	22		7		29

treatment with corticosteroids, civamide or botulinum toxin A, previous treatment within 24 hours prior to the beginning of the study or concomitant treatment with other triptans including treatment of acute attacks with subcutaneous sumatriptan, ergotamine, ergotamine derivatives or other 5-HT₁-receptor agonists.

RESULTS

The study was prematurely discontinued after 13 months and enrollment of 11, instead of the planned 80 patients, by the sponsor due to infeasibility. Recruitment was slow and each of the patients included conducted major protocol violations. All protocol violations are summarized in Table 1. The most common protocol deviations included violation of exclusion criteria (primarily #18, concomitant

Table 2.—Frequency of Cluster Headache Attacks

Treatment	n	Headache Cluster Frequency (Per Week)					
		Run in		Treatment Period			
		Mean	STD	Mean	STD	95% CI	<i>P</i>
Frovatriptan	4	14.8	7.3	14.1	6.8	3.4,24.9	0.6095
Placebo	6	16.2	9.9	10.1	10.1	-0.5,20.7	

treatment with other triptans) and intake of prohibited medication, mainly to treat cluster attacks.

Medical History and Demographic Characteristics.—The medical history and demographic characteristics of all patients at baseline were comparable between the 2 groups except for weight and body mass index, which both were higher in the frovatriptan group.

Efficacy Results.—The mean cluster headache frequency per week during treatment (primary endpoint) was higher in the frovatriptan than in the placebo group (14.1 vs 10.1). The difference was not significant (Table 2).

In the frovatriptan group was 1 and in the placebo group were 4 responders regarding cluster headache attack frequency (25% vs 66.7%). Response was defined as a reduction of the mean number of cluster headache attacks per week by at least 50%.

The frequency of headache attacks per week continuously decreased over the time with placebo but remained rather constant with frovatriptan. The attack frequency during run-in, first treatment week, second treatment week and follow up was in the frovatriptan group: 15, 14, 14, 11 attacks and in the placebo group 16, 12, 8, 3 attacks.

Mean attack duration was shortened with frovatriptan from 56 to 41 minutes but not with placebo treatment.

With regard to quality of life, placebo-treated patients performed better than frovatriptan-treated patients for almost all scores.

For all other secondary variables no differences were apparent.

Safety Results.—During the 14-day treatment period, there was no adverse event (AE) in the frovatriptan group. However, 6 AEs in 4 patients of the placebo group were reported during this period.

DISCUSSION

Only few drugs are available for the prophylactic treatment of cluster headaches. This study shows that particular therapeutic aims are impossible to be addressed in a double-blind, randomized, parallel group, study design with specific inclusion and exclusion criteria according to the IHS-guidelines for controlled trials of drugs in cluster headache.¹⁵ The trial, its design and the analysis of why the trial failed may teach important lessons for future trial design in cluster headache. The study was terminated by the sponsor due to the fact that not enough eligible patients could be enrolled at almost all study centers. Over a recruitment period of 13 months, recruitment was very slow and all of the 11 patients enrolled conducted major protocol violations. Hence, conclusions about the efficacy of frovatriptan cannot be drawn. The dosage of 5 mg frovatriptan, however, appeared safe and was well tolerated although only used by 4 patients. Following these experiences, we suggest to adjust and discuss the recommendations of the guidelines for controlled trials of drugs in cluster headache from the IHS to improve the likelihood for successful trial conduct.

REASONS FOR SLOW RECRUITMENT AND PROTOCOL DEVIATIONS

The trial was designed according to the Guidelines for Controlled Trials of Drugs in Cluster Head-

ache of the IHS¹⁵ and in addition, consultations of the sponsor with the responsible authority in Germany (BfArM) took place to ensure that the trial would qualify as one of several (still to be conducted) trials in a future approval process. Criteria used in our trial reflect the necessary safety standards to avoid interactions with concomitant medication.

1. Concomitant medication for prophylactic therapy as well as for acute treatment, eg, concomitant prophylactic treatment with corticosteroids was not allowed. In real life, corticosteroids are popular and are given at the beginning of a cluster episode to a high percentage of patients.
2. Treatment of acute attacks with subcutaneous sumatriptan: this was not allowed to avoid triptan overdosing. Because ECH is one of the most severe pain conditions, patients need a fast pain relief. Strict compliance, especially nonuse of sumatriptan, cannot be expected from patients. Therefore, it is not surprising that patients in this situation are more likely to conduct protocol violations rather than to suffer from unbearable pain.
3. Concomitant usage of triptans or ergots: in this study, frovatriptan should be investigated as a prophylactic agent. Hence, the usage of other triptans or ergots 24 hours prior and during the study was prohibited for safety reasons. For treatment of acute cluster attacks, the inhalation of pure oxygen was permitted, but the majority of patients not responding to oxygen insisted on the use of 5-HT_{1B/D}-agonist sumatriptan sc for attack termination and was therefore not interested in participating in this trial. Particularly, this could have been the main reason for the slow recruitment.
4. Another multitude of patients use triptans or other forbidden medication during study or prior enrollment due to the fact that supply with oxygen for patients with cluster headache in Germany is poor, and many patients who have an oxygen-inhalator for home use don't have portable equipment for use, eg, at work.
5. Restart of prophylactic medication without consulting: many patients with ECH reduce the dosage of prophylactic medication or discontinue drugs in the headache free intervals. With a new

- cluster episode many patients increase the dose of their prophylactic medication again or restart previous medication on their own decision and without consulting their physician. This behavior reduced the potential number of patients for the trial significantly, because one of the main exclusion criteria was "change in concomitant prophylactic medication one month prior to visit one."
6. Duration of cluster episode: the duration of the episodes can vary, the mean duration of episodes is 8.6 weeks.¹⁶ To fulfill the recommended inclusion criteria, patients must have suffered from attacks already for one week. Further to this, the expected duration of the current episode should be at least 6 weeks from screening, which implies a necessary duration of the current episode of at least 7 weeks. In many cases the appearance of the first attack was more than 1 week ago. For this reason a significant number of patients with short cluster episodes of few weeks could not be enrolled (inclusion criteria #5 and #6).

CONCLUSION

With only 11 patients included who all presented with major protocol deviations, the study was not able to show significant differences between treatment groups. No significant differences or trends were observed neither for the primary nor any secondary efficacy parameter. With regard to safety, there was neither any AE in the frovatriptan-group during treatment nor any treatment related effects on vital signs, electrocardiogram, or clinical laboratory. The treatment was safe and well tolerated.

The failure of this trial should not discourage from testing frovatriptan in this indication, if a rescue medication other than oxygen is available.

To show efficacy of triptans in the prophylactic treatment of ECH further studies are required. The recommendations of the Guidelines for controlled Trials of Drugs in Cluster Headache from the IHS should be revised.

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