A review of the use of frovatriptan in the treatment of menstrually related migraine

Gianni Allais and Chiara Benedetto

Ther Adv Neurol Disord

(2013) 6(2) 55–67

DOI: 10.1177/
1756285612470191

© The Author(s), 2012.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Menstrual migraine (MM) is a highly prevalent condition associated with considerable disability. Migraine attacks occur exclusively around the menstrual period in approximately 10% of women with migraine, that is, pure menstrual migraine, while at least 50% of them also experience migraine at other times of the month, that is, menstrually related migraine (MRM). The therapeutic approach to patients with MRM is based on treatment of the attack, or prophylactic strategies. Triptans are recommended as first-line treatments for moderate to severe migraine attacks, including MM. Frovatriptan is one of the newest triptans. Its high affinity for 5-HT_{1B/1D} receptors and long half-life contribute to its distinctive clinical effect, characterized by a more sustained and prolonged effect than other triptans. Indeed, frovatriptan proved to be effective in treating the acute attack, but was particularly effective in the short-term preventive therapy of MM. In addition, frovatriptan is one of the safest triptans, with the lowest risk of treatment-emergent adverse events. Following extensive evidence from randomized pharmacological trials, frovatriptan has now gained a grade A recommendation from the guidelines for short-term prophylaxis of MM. Recent *post-hoc* analyses of direct comparative trials also suggest that frovatriptan might have an important role in the acute treatment of MRM. In these studies, frovatriptan showed pain relief and pain-free rates similar to those of zolmitriptan, rizatriptan, and almotriptan, but with significantly lower recurrence rates. More well-designed, randomized, prospective studies, specifically enrolling women with MM, will be needed in the near future to confirm the efficacy of frovatriptan in this migraine subtype.

Keywords: frovatriptan, menstrual migraine, menstrually related migraine

Introduction

The International Headache Society defines menstrually related migraine (MRM) as attacks of migraine without aura in a menstruating woman, occurring on day 1 ± 2 of menstruation (namely between 2 days before menstruation and the first 3 days of bleeding) in at least two out of three menstrual cycles and additionally at other times of the cycle [Headache Classification Subcommittee of the International Headache Society, 2004]. Menstruation is usually defined by endometrial bleeding resulting from either the normal menstrual cycle, or from the withdrawal of exogenous progestogens, as in the case of combined oral contraceptives and cyclical hormone replacement therapy. Migraine attacks occur exclusively around the menstrual period in approximately 10% of women, that is, pure menstrual migraine (PMM), while at least half of women with migraine experience MRM [MacGregor, 2008; Martin and Lipton, 2008; Taylor, 2009].

Migraine attacks occurring during menses, generally classified as menstrual migraine (MM), represent a challenge for both the patient and the headache specialist as they are particularly difficult to manage and more disabling than migraines outside the menstrual period [Allais *et al.* 2007].

The purpose of this review is to provide an overview on the efficacy of frovatriptan in the acute and preventive treatment of MM in the light of recent publications and indications from guidelines [Silberstein *et al.* 2012; Steiner *et al.* 2007].

Current therapeutic approach to MM

The therapeutic approach to patients with MRM is based on treatment of the symptoms of attack, or with prophylactic strategies [Silberstein *et al.* 2012; Steiner *et al.* 2007].

Correspondence to:
Gianni Allais, MD
Women's Headache
Center, Department
of Gynecology and
Obstetrics, University of
Turin, Via Ventimiglia 3,
10126 Turin, Italy
gb.allais@tiscali.it

Chiara Benedetto, MD, PhD
Women's Headache
Center, Department of
Gynecology and Obstetrics,
University of Turin, Turin,
Italy

The goal of acute treatment is to attenuate or remove symptoms, and this approach is ideal for infrequent attacks. No drugs are specifically approved for the acute treatment of MRM. However, treatments licensed for migraine are usually indicated also for the treatment of MM [Headache Classification Subcommittee of the International Headache Society, 2004]. The current therapeutic armamentarium against acute MM is the same as for nonmenstrual attacks, and includes triptans, nonsteroidal anti-inflammatory drugs, ergot derivatives, or a combination of analgesics with or without prokinetic antiemetics [MacGregor, 2010].

Prophylaxis may be an option for treating MM, but its choice depends on the frequency, duration, and severity of attacks, as well as on the response to acute treatment [Tepper, 2006]. The goal of preventive treatment is to reduce attack frequency, severity, and duration, improve responsiveness to treatment of acute attacks, ameliorate function, and reduce disability [Pringsheim *et al.* 2008]. Currently suggested effective prophylaxis is based on nonsteroidal anti-inflammatory drugs, perimenstrual administration of estrogen or triptans, but no treatment is at the moment licensed for MM prevention. The current opinion is that an empirical approach is usually necessary, trying different interventions before considering the effective prophylactic program. Prophylaxis seems to be particularly suited for those women experiencing inadequate relief from the usual forms of acute therapy, or who are troubled by headache recurrence and require multiple doses of acute migraine medications [Tepper, 2006; Pringsheim *et al.* 2008], or for those women with regular menses and predictable crisis [Allais *et al.* 2007]. The choice between short-term (perimenstrual) and continuous prophylaxis depends on the individual woman's type of migraine, regularity of menstruation, other menstrual problems, and need for contraception [MacGregor, 2010]. Usually, short-term prevention is preferred to long-term prophylaxis, because it potentially reduces the risk of adverse events.

Triptans and migraine

Triptans are serotonin 5-HT_{1B/1D} receptor agonists acting on several areas, both around vasculatures and centrally [Loder, 2010]. They provide relief from migraine pain by cranial vasoconstriction, most likely through action at postsynaptic 5-HT_{1B} receptors on the smooth-muscle cells of

meningeal blood vessels. They also act at presynaptic 5-HT_{1D} receptors on trigeminal nerve terminals projecting peripherally to the dural vasculature and centrally to the brainstem trigeminal nuclei [Loder, 2010; Kalra and Elliott, 2007]. 5-HT receptors are also localized on glutamate-positive trigeminal neurons: triptans could reduce glutamate release by acting through these receptors and this may contribute to their therapeutic effect [Ramadan *et al.* 2003].

Seven triptans are available worldwide, in different strengths and formulations, including oral tablets, orally disintegrating tablets or wafers, nasal sprays, subcutaneous injections, and suppositories (Table 1). Specific pharmacological and clinical differences among the triptans exist [Loder, 2010; Ferrari *et al.* 2002; Bigal *et al.* 2003; Johnston and Rapoport, 2010; Pascual *et al.* 2007]. The first triptan to be developed, sumatriptan, offers the most rapid and complete pain relief when administered subcutaneously, but is also associated with a higher incidence of adverse events. Pharmacology of second-generation triptans was modeled on sumatriptan, aiming at developing oral formulations with improved bioavailability, and increased rate of drug absorption potentially to hasten and improve migraine headache relief [Rapoport *et al.* 2003]. All triptans are superior to placebo in clinical trials, and some (zolmitriptan, rizatriptan, almotriptan, and eletriptan) are similar to each other and the prototype, sumatriptan (Table 1). These triptans are known as fast-acting triptans and are characterized by a faster onset of action, but also a higher risk of adverse events and a higher recurrence rate (Table 1). Naratriptan and frovatriptan belong to the group with lower recurrence and a better tolerability (Table 1).

Use of triptans in MM

Triptans are recommended as first-line treatment for moderate to severe migraine, hence including MM [Taylor, 2009; Mannix and Files, 2005].

Data from randomized, placebo-controlled or active-treatment comparative studies for the acute treatment of MM are available for all seven triptans currently approved and licensed. Evidence of triptan efficacy for short-term prophylaxis is consistent only for naratriptan [Mannix *et al.* 2007; Moschiano *et al.* 2005; Newman *et al.* 2001; Brandes *et al.* 2007], and frovatriptan [Silberstein *et al.* 2004, 2009;

Table 1. Pharmacologic and clinical characteristics of triptans and main efficacy results from clinical trials.

	Sumatriptan	Zolmitriptan	Rizatriptan	Naratriptan	Almotriptan	Eletriptan	Frovatriptan
Formulations	Tablets (nasal spray, subcutaneous injection, suppositories)	Tablets (oral wafer, nasal spray)	Tablets (oral wafer)	Tablets	Tablets	Tablets	Tablets
Commonly prescribed dose for tablets	50–100 mg	5 mg	10 mg	1–2.5 mg	12.5 mg	20–40 mg	2.5 mg
T _{max} (h)	2.5	2	1.2	2–3	1.4–3.8	1–2	2–4
Lipophilicity	Low	Moderate	Moderate	High	Low	High	Low
Half-life (h)	2–2.5	2.5–3	2–3	5–6	3–4	4–5.5	25–26
Bioavailability (%)	14	40–48	45	63–74	80	50	24–30
Elimination route and metabolism for triptan tablets	Hepatic Monoamine oxidase-A 60% renal	Hepatic Cytocrome P450	Hepatic Monoamine oxidase-A 30% renal	Cytocrome P450 70% renal	Hepatic Monoamine oxidase-A Cytocrome P450 26–35% renal	Hepatic	Hepatic Monoamine oxidase-A Cytocrome P450 26–35% renal
Minimum interval between repeating dose for tablets (h)	2	2	2	4	2	2	2
Maximum daily dose for tablets	200 mg	10 mg	30 mg	5 mg	25 mg	80 mg	7.5 mg
Rapid onset	+	+	+	-	+	+	-
High potency	+	+	+	-	+	+	-
Low recurrence	-	-	-	+	-	-	+
Good tolerability	-	-	-	+	+	-	+

T_{max}, time to reach peak plasma concentration.

Brandes *et al.* 2009; Guidotti *et al.* 2007], while it is limited for sumatriptan [Newman *et al.* 1998], and zolmitriptan [Tuchman *et al.* 2006, 2008], and lacking for other triptans.

Main efficacy and safety endpoints of acute treatment studies reporting on conventional efficacy endpoints (i.e. pain relief, pain free, sustained pain free, and recurrence) are summarized in Table 2. Data reported in this table were identified through a Medline database search from inception to May 2012. Retrieved publications were evaluated for relevance to this review. No formal meta-analytic approach was deliberately applied, and the review was kept intentionally descriptive.

All triptans seem to be effective in the acute treatment of MRM, with no significant difference in their efficacy in the treatment of menstrual *versus* nonmenstrual attacks. Also the trials using triptans for perimenstrual prophylaxis have suggested efficacy, particularly for naratriptan and frovatriptan. However, most of the studies were *post-hoc* analyses of efficacy trials, which were not originally specifically undertaken in women with MM, and in which treatment within or outside a specified temporal menstrual window is reported. Some trials evaluated MRM attacks, others PMM attacks. Some studies treated only moderate or severe attacks, while other studies also treated mild attacks.

Table 2. Summary of studies evaluating efficacy according to traditional endpoints and safety of acute treatment of various triptans orally administered in menstrual migraineurs.

Author, year	Study design	Drug	Dose (mg)	n	PR 2 h (%)	PF 2 h (%)	R 24 h (%)	SPF 24 h (%)	AE (%)
Sumatriptan									
Nett <i>et al.</i> [2003]	DB, PG, PC	Sumatriptan	50	116	-	51	-	30	3*
Nett <i>et al.</i> [2003]	DB, PG, PC	Sumatriptan	100	115	-	61	-	31	11*
Landy <i>et al.</i> [2004]	DB, PG, PC	Sumatriptan	50	138	-	51	-	30	13
Landy <i>et al.</i> [2004]	DB, PG, PC	Sumatriptan	100	133	-	58	-	35	20
Schreiber and Cady [2007]	OL	Sumatriptan	100	39	70	41	-	-	-
Facchinetti <i>et al.</i> [2010]	DB, CO	Sumatriptan	50	135	66	27	66	-	-
				676	66-70	27-61	66	30-35	3-20
Zolmitriptan									
Loder <i>et al.</i> [2004]]	DB, PG, PC	Zolmitriptan	1.25-15	260	48	26	32	-	16*
Tuchmann <i>et al.</i> [2006]	DB, PG, PC	Zolmitriptan	2.5	174	66	28	29	-	63
Allais <i>et al.</i> [2006]	DB, PG, <i>post-hoc</i> analysis	Zolmitriptan	2.5-5	119	69	41	35	27	18*
Allais <i>et al.</i> [2011b]	DB, CO, <i>post-hoc</i> analysis	Zolmitriptan	2.5-5	76	53	26	22	-	-
				629	48-69	26-41	22-35	27	16-63
Rizatriptan									
Silberstein <i>et al.</i> [2000]	DB, CO, <i>post-hoc</i> analysis	Rizatriptan	10	534	68	42	36	-	-
Silberstein <i>et al.</i> [2000]	DB, CO, <i>post-hoc</i> analysis	Rizatriptan	5	509	70	33	44	-	-
Silberstein <i>et al.</i> [2002]	OL (randomized), PG, PC, <i>post-hoc</i> analysis	Rizatriptan	10-20	95	78	48	32	32	-
Nett <i>et al.</i> [2008]	DB, PG, PC	Rizatriptan	10	480	71	39	-	24	14*
Martin <i>et al.</i> [2008]	DB, PG, PC, <i>post-hoc</i> analysis	Rizatriptan	10	63	-	64	-	-	-
Savi <i>et al.</i> [2011]	DB, CO, <i>post-hoc</i> analysis	Rizatriptan	10-20	93	64	34	32	-	-
				1774	64-78	33-64	32-44	24-32	14
Naratriptan									
Massiou <i>et al.</i> [2005]	DB, PG, PC	Naratriptan	2.5	115	58	43	-	42	3*
Almotriptan									
Allais <i>et al.</i> [2008]	DB, PG, <i>post-hoc</i> analysis	Almotriptan	12.5-25	136	68	45	33	29	13*
Diamond <i>et al.</i> [2008]	DB, PG, PC, <i>post-hoc</i> analysis	Almotriptan	12.5	97	77	35	-	29	-
Allais <i>et al.</i> [2011a]	DB, CO, PC	Almotriptan	12.5-25	74	-	48	29	36	6*
Bartolini <i>et al.</i> [2012]	DB, CO, <i>post-hoc</i> analysis	Almotriptan	12.5-25	67	41	29	21	-	-
				374	41-77	29-48	21-33	29-36	6-13

Table 2. (Continued)

Author, year	Study design	Drug	Dose (mg)	n	PR 2 h (%)	PF 2 h (%)	R 24 h (%)	SPF 24 h (%)	AE (%)
Frovatriptan									
Allais <i>et al.</i> [2008]	OL	Frovatriptan	2.5–5	20	55	-	36	-	-
Allais <i>et al.</i> [2011b]	DB, CO, <i>post-hoc</i> analysis	Frovatriptan	2.5–5	76	52	22	15	-	-
Savi <i>et al.</i> [2011]	DB, CO, <i>post-hoc</i> analysis	Frovatriptan	2.5–5	93	58	31	10	-	-
Bartolini <i>et al.</i> [2012]	DB, CO, <i>post-hoc</i> analysis	Frovatriptan	2.5–5	67	36	19	8	-	-
				256	36–55	19–31	8–36	-	-
*Drug-related AE.									
AE, adverse event; CO, cross over; DB, randomized double blind; OL, nonrandomized open label; PC, placebo-controlled; PF, pain free; PG, parallel group; PR, pain relief; R, recurrence; SPF, sustained pain free.									

Heterogeneity in drug doses and treatment duration also limited the robustness of the interpretation of results.

Evidence from recent systematic reviews and meta-analyses of randomized trials supports a grade B recommendation for the use of sumatriptan 50 mg and 100 mg, or sumatriptan 85 mg plus naproxen 500 mg, or rizatriptan 10 mg for the acute treatment of MM [Pringsheim *et al.* 2008; Mannix and Files, 2005]. With respect to prophylaxis, there is grade A evidence of efficacy for short-term treatment with frovatriptan 2.5 mg twice daily, and grade B for naratriptan 1 mg twice daily [Silberstein *et al.* 2012]. In the case of preventive treatment, attention should be paid to avoid treatment overuse, which may defer attacks or even result in rebound migraine following withdrawal.

Pharmacologic features of frovatriptan

Frovatriptan is one of the newest agents of the triptan class. The drug was developed in order to provide a triptan with the clinical potential for a long duration of action, and a low likelihood of side effects and drug interactions [Balbisi, 2006]. The drug has distinctive pharmacologic features compared with other triptans, which make it particularly well suited to patients with prolonged migraines and those suffering migraine recurrence, such as patients with MM (Table 1) [Balbisi, 2006].

Frovatriptan has a potent affinity for 5-HT_{1B} and 5-HT_{1D} receptors, the highest among agents of the same class, and a higher selectivity for the cerebral vasculature, with minimal effects on coronary circulation [Comer, 2002]. The mean blood terminal deposition half-life of frovatriptan is approximately 26 h, the longest among agents within its class, and is not affected by gender, dose, or route of administration [Buchan *et al.* 2002]. In addition, due to the lack of inhibitory or inducing effects on cytochrome P450 isoenzymes, frovatriptan retains a low risk of drug interactions, and dosage adjustment is unlikely to be warranted. This is particularly relevant, since combination treatment of frovatriptan with analgesic drugs is sometimes required.

All these elements seem to contribute to the distinctive pharmacologic properties of frovatriptan, reflecting in particular clinical efficacy and safety in MM, summarized below.

Efficacy of frovatriptan in the prevention of MM: evidence from randomized controlled studies

Scheduled short-term preventive frovatriptan therapy effectively reduced the occurrence of MM in women with attacks occurring in association with menstruation in a number of randomized, controlled trials (Table 3).

In a randomized, double-blind, placebo-controlled, three-way cross-over study, 546 women treated three perimenstrual periods with placebo, frovatriptan 2.5 mg once daily, and frovatriptan 2.5 mg twice daily [Silberstein *et al.* 2004]. Treatment started 2 days before the anticipated start of MM headache and lasted for 6 days. Both frovatriptan regimens were superior to placebo, with a dose-dependent reduction in the incidence of migraine. Overall, the incidence of headache was 67% in subjects receiving placebo, 52% in those receiving frovatriptan 2.5 mg once daily, and 41% in those receiving frovatriptan 2.5 mg twice daily. Both active treatment regimens significantly ($p < 0.001$) reduced the incidence of all-severity headache, but also the incidence of moderate or severe headache (28–37% frovatriptan *versus* 51% placebo, $p < 0.0001$), duration (16.6–20.3 h frovatriptan *versus* 31.1 h placebo, $p < 0.0001$), and the use of rescue medication (34–44% frovatriptan *versus* 53% placebo, $p < 0.01$) compared with placebo. The incidence and type of adverse events were similar between active treatment (42.9% frovatriptan 2.5 mg once daily and 44.3% frovatriptan twice daily) and placebo (40.2%), and consistent with those reported for short-term migraine management.

More recently the same authors run a *post-hoc* analysis of the same study in a subgroup of 179 women with PMM [Silberstein *et al.* 2009]. Also in this sample of migraineurs, a preventive regimen with frovatriptan significantly reduced the occurrence of headache to 37.7% with frovatriptan 2.5 mg twice daily ($p < 0.001$ *versus* placebo), to 51.3% with frovatriptan 2.5 mg once daily ($p = 0.002$), and to 67.1% with placebo. A significant dose response was noted also in this case.

Treatment with frovatriptan 2.5 mg once or twice daily was associated with a significantly increased number of headache-free perimenstrual periods (0.92 and 0.69, $p < 0.001$ and $p < 0.02$, respectively) compared with placebo (0.42) in a double-blind, placebo-controlled, parallel-group trial, enrolling 410 women with difficult-to-treat MM

[Brandes *et al.* 2009]. Frovatriptan also reduced migraine severity.

From all this evidence, a grade A recommendation for short-term treatment with frovatriptan 2.5 mg twice daily has recently been made [Silberstein *et al.* 2012].

Frovatriptan in the acute treatment of MM: evidence from randomized controlled studies

The efficacy of frovatriptan for the treatment of acute migraine attack has been recently assessed with that of other triptans in three different randomized, double-blind, cross-over studies. All studies had an identical design. *Post-hoc* analyses of such studies were recently published [Allais *et al.* 2012]; they were performed in women with MRM, defined according to International Headache Society criteria [Headache Classification Subcommittee of the International Headache Society, 2004]. Each patient received frovatriptan 2.5 mg or the comparator (rizatriptan 10 mg, zolmitriptan 2.5 mg, or almotriptan 12.5 mg) in a randomized sequence: after treating three episodes of migraine in no more than 3 months with the first treatment, the patient had to switch to the other treatment. Subjects were encouraged to treat one to three attacks for a maximum period of 6 months. Pain relief was defined as a decrease in migraine intensity from severe or moderate to mild or none at 2 h and 24 h, pain free as absence of migraine episodes at 2 h and 24 h after intake of one dose of the study drug, and recurrence as a pain-free episode at 2 h and headache of any severity returning within 24 h and 48 h. As shown in Figure 1, the rate of pain relief and pain free at 2 h and 24 h were not significantly different between frovatriptan and each individual comparator. In order to obtain pain free at 2 h the number of additional patients to be treated with frovatriptan was 33 *versus* rizatriptan, 25 *versus* zolmitriptan, and 10 *versus* almotriptan. Recurrence at 24 h (Figure 1), and even more so at 48 h (Figure 2) was always significantly lower with frovatriptan than with the other triptans. The numbers needed to treat to reduce the risk of recurrence at 24 h were favorable for frovatriptan (5 fewer than rizatriptan, 14 fewer than zolmitriptan, and 8 fewer than almotriptan). Similarities and differences between treatments were more striking when data were pooled (bottom panel of Figures 1 and 2). The numbers needed to treat to obtain pain free at 2 h were 14 *versus* comparators, while recurrence at 24 h was prevented treating 9 fewer patients with frovatriptan.

Table 3. Summary of randomized controlled and open-label studies evaluating preventive or acute efficacy of frovatriptan for the treatment of menstrual migraine.

Author, year	Type of treatment	Study design	n	Type of subjects	Active treatment	Control	Treatment period	Main results
Silberstein <i>et al.</i> [2004]	Prophylactic	DB, CO	506	MRM	F 2.5 mg once daily and F 2.5 mg twice daily	Placebo	6 days, 3 perimenstrual periods	F significantly reduced the occurrence of migraine, its severity and duration, and the use of rescue medication compared with placebo. Safety of F comparable to that of placebo.
Guidotti <i>et al.</i> [2007]	Prophylactic	OL, PG	38	MRM	F 2.5 mg once daily	Transdermal estrogen 25 µg once daily Naproxen sodium 500 mg once daily	6 days, 3 perimenstrual periods	F significantly reduced daily incidence and severity of migraine compared with controls.
Silberstein <i>et al.</i> [2009]	Prophylactic	DB, CO (<i>post-hoc</i> analysis)	179	PMM	F 2.5 mg once daily and F 2.5 mg twice daily	Placebo	6 days, 3 perimenstrual periods	F significantly reduced the occurrence of migraine compared with placebo.
Brandes <i>et al.</i> [2009]	Prophylactic	DB, PG	410	MRM	F 2.5 mg once daily and F 2.5 mg twice daily	Placebo	6 days, 3 perimenstrual periods	Headache-free treatment periods significantly greater and migraine severity lower with F than with placebo.
Allais <i>et al.</i> [2008]	Acute	OL	20	OCMM	F 2.5 mg	None	7 days (pill-free period)	F significantly decreased headache intensity and increased rate of pain free and pain relief at 2, 4 and 24 h, and decreased risk of recurrence at 24 h.
MacGregor <i>et al.</i> [2010]	Acute	OL (<i>post-hoc</i> analysis)	151	MRM	F 2.5 mg	None	6 months	F was rated as good or very good by the majority of women.
Savi <i>et al.</i> [2011]	Acute	DB, CO (<i>post-hoc</i> analysis)	93	MRM	F 2.5 mg	Rizatriptan 10 mg	3 months, 3 episodes	Rate of pain free and pain relief at 2 and 24 h similar between F and rizatriptan, recurrence at 24 h significantly lower with F.
Allais <i>et al.</i> [2011b]	Acute	DB, CO (<i>post-hoc</i> analysis)	76	MRM	F 2.5 mg	Zolmitriptan 2.5 mg	3 months, 3 episodes	Rate of pain free and pain relief at 2 and 24 h similar between F and zolmitriptan, recurrence at 24 h significantly lower with F.

(Continued)

Table 3. (Continued)

Author, year	Type of treatment	Study design	n	Type of subjects	Active treatment	Control	Treatment period	Main results
Bartolini et al. [2012]	Acute	DB, CO (post-hoc analysis)	67	MRM	F 2.5 mg	Almotriptan 12.5 mg	3 months, 3 episodes	Rate of pain free and pain relief at 2, 4 and 24 h similar between F and almotriptan, recurrence at 24 and 48 h significantly lower with F.
Allais et al. [2012]	Acute	DB, CO (post-hoc analysis)	187	MRM	F 2.5 mg	Rizatriptan 10 mg Zolmitriptan 2.5 mg Almotriptan 12.5 mg	3 months, 3 episodes	Rate of pain free and pain relief at 2, 4 and 24 h similar between F and comparators, recurrence at 24 and 48 h significantly lower with F.
CO, cross over; DB, randomized double blind; F, frovatriptan; MRM, menstrually related migraine; OCMM, oral contraceptive-induced menstrual migraine 0L, nonrandomized open label; PG, parallel group; PMM, pure menstrual migraine.

Figure 1. Frequency (%) of PR at 2 h and 4 h, PF at 2 h and 4 h, and R at 24 h in patients treated with frovatriptan (open bars) or rizatriptan, zolmitriptan, almotriptan or the three triptans pooled together (full bars). Data refer to three different double-blind, randomized, cross-over studies. *p*-values indicate the statistical significance of the between-treatment difference [Savi *et al.* 2011; Allais *et al.* 2011b; Bartolini *et al.* 2012]. PF, pain free; PR, pain relief; R, recurrence.

Figure 2. Cumulative hazard of recurrence over the 48 h of treatment with frovatriptan (continuous line) or comparators (dashed line) in 187 patients of three double-blind, randomized, cross-over studies. *p*-value refers to the statistical significance of the between-treatment difference [Allais *et al.* 2012].

Table 4. Demographic and clinical characteristics and main efficacy parameters for the whole population of three randomized controlled studies comparing frovatriptan with rizatriptan, zolmitriptan, or almotriptan, and for the subgroup of women with menstrually related migraine [Allais *et al.* [2012]; Cortelli *et al.* [2011]].

	Main study (n = 346)	Subgroup of menstruating women (n = 187)	p-value
Age (years, mean $\pm$ SD)	38 $\pm$ 10	36 $\pm$ 8	NS
Age at onset of migraine (years, mean $\pm$ SD)	17 $\pm$ 7	16 $\pm$ 6	NS
Migraine attack duration >2 days (n, %)	72 (21)	42 (22)	NS
No use of triptans in the previous 3 months (n, %)	146 (42)	83 (44)	NS
Patients with at least one moderate or severe attack (n, %)	334 (97)	179 (96)	NS
Frovatriptan			
PR 2 h (n / number of treated attacks, %)	439 / 794 (55)	74 / 199 (37)	<0.01
PF 2 h (n / number of treated attacks, %)	296 / 988 (30)	46 / 199 (23)	NS
R 48 h (n / number of treated attacks, %)	79 / 296 (27)	29 / 199 (15)	<0.01
Comparators			
PR 2 h (n / number of treated attacks, %)	452 / 772 (59)	87 / 202 (43)	<0.01
PF 2 h (n / number of treated attacks, %)	339 / 990 (34)	60 / 202 (30)	NS
R 48 h (n / number of treated attacks, %)	135 / 339 (40)	53 / 202 (26)	<0.01

NS, not significant; SD, standard deviation.

Interestingly, the response to treatment with frovatriptan or the comparators was less potent in menstruating women than in the whole study population, confirming that MM attacks are particularly difficult to treat (Table 4).

Efficacy of frovatriptan in MM: evidence from open-label studies

There are also some open-label studies confirming the efficacy of frovatriptan as preventive or acute treatment for MM attacks.

A small pilot, non-randomized, parallel group study compared the preventive efficacy of frovatriptan *versus* that of transdermal estrogens or naproxen in 38 women with MM [Guidotti *et al.* 2007]. Daily incidence of migraine was significantly ($p = 0.045$) lower under frovatriptan than under control treatments, this being particularly evident for the subgroup of patients with PMM (60% frovatriptan *versus* 79% estrogens and 78% naproxen sodium). During treatment the median score of headache severity was significantly ($p = 0.049$) lower under frovatriptan (2.5) than under estrogen (3.0) or naproxen treatment (3.9).

In an open-label study 151 menstrually capable patients were enabled to take up to three tablets of frovatriptan 2.5 mg over a 24-h period to treat an acute attack. Migraine relief within 24 h was

achieved in 82% of menstrual attacks and 87% of nonmenstrual attacks. The time to overall relief was longer in menstrual attacks (5.5 h *versus* 3.6 h nonmenstrual attacks) [MacGregor *et al.* 2010].

Another open-label, uncontrolled pilot study, evaluated the efficacy of frovatriptan 2.5 mg in 20 women with oral contraceptive-induced MM [Allais *et al.* 2008]. Frovatriptan was administered during the 7 days off oral contraceptive at the onset of a moderate or severe migraine attack. A second dose could be taken if symptoms were alleviated but recurred within 24 h. After administration of frovatriptan the headache intensity progressively and significantly ($p = 0.0001$) decreased from 2.4 at onset to 0.8 after 24 h. A total of 10% of subjects were pain free at 2 h, 35% at 4 h, and 60% at 24 h, while pain relief was reported after 2 h by 55% of patients and by 75% after 4 h and 24 h. Headache recurred within 24 h in 36% of patients.

Finally we should mention an open-label post-marketing surveillance study conducted in 1931 women with MM and 2080 women with non-menstrual migraine [Newman *et al.* 2009]. The study was a retrospective analysis of an acute treatment study. Previous medications were rated at baseline as good or very good for effectiveness by only 20% of menstrual migraineurs and 19% of nonmenstrual migraineurs, while the

corresponding figure after frovatriptan treatment was 93% and 91%, respectively.

All the randomized controlled and open-label studies based on frovatriptan and described in the previous paragraphs were financially supported by the manufacturers of frovatriptan (Berlin-Chemie AG, Berlin, Germany; Endo Pharmaceuticals Inc., Chadds Ford, PA, USA; Vernalis Development Ltd., Wincoburn, UK; Istituto Lusofarmaco d'Italia, Milan, Italy).

Safety of frovatriptan in MM

Safety and tolerability of frovatriptan as short-term preventive therapy or acute treatment for MM have been extensively studied.

A pooled analysis of three studies including 1487 women with MM has evaluated the long-term safety of frovatriptan prophylactic treatment in up to 12 perimenstrual periods over a 12- to 15-month period [MacGregor *et al.* 2009; MacGregor *et al.* 2010]. Adverse events were reported in 58% of women treated with frovatriptan 2.5 mg twice daily, in 63% of those treated with frovatriptan once daily, and in 63% of those receiving placebo, with no between-group differences. There were no consistent differences in adverse events reported by patients with potential cardiovascular risk. In no cases was a dose relationship for adverse events observed. No cardiovascular safety issues resulted from repeated dosing, nor was there evidence of rebound migraine after withdrawal of frovatriptan at the end of the treatment period.

In the pooled analysis of the three direct comparative studies of frovatriptan *versus* other triptans, a total of 18 drug-related adverse events were recorded in 401 menstrually related attacks treated [Allais *et al.* 2012]. No statistically significant differences were observed in the rate of attacks associated with drug-related adverse events between frovatriptan (5%) and the comparators (4%).

Conclusion

Frovatriptan has been found in a number of trials to be effective in the acute treatment of MRM. In particular, direct comparative studies evaluating approximately 200 women with MM have shown a similar immediate antimigraine efficacy profile of frovatriptan, zolmitriptan, rizatriptan, and almotriptan. However, frovatriptan treatment was associated with a more sustained relief effect on

migraine with lower headache recurrence rates over 24 h, and even more so over 48 h [Savi *et al.* 2011; Allais *et al.* 2011b; Bartolini *et al.* 2012]. Such differences might be explained, at least in part, by differences in the pharmacokinetics of frovatriptan in respect to the other triptans. Frovatriptan has a longer elimination half-life than rizatriptan, zolmitriptan, and almotriptan, possibly explaining why frovatriptan, unlike the other tested triptans, greatly reduced the risk of recurrence [Loder, 2010].

Frovatriptan given prophylactically for 6 days was effective in reducing the incidence of MM in approximately half of the 1100 women treated with the drug [Silberstein *et al.* 2004; Silberstein *et al.* 2009; Brandes *et al.* 2009; Guidotti *et al.* 2007]. These findings are consistent with the prolonged duration of action of frovatriptan that has been observed in studies of acute migraine treatment.

Unfortunately, most of the studies performed so far with frovatriptan in MRM share a *post-hoc* nature. However, their positive results encourage the design and implementation of large, double-blind, randomized, prospective clinical trials specifically evaluating frovatriptan efficacy in MRM.

Frovatriptan was as well tolerated as the other triptans, with a low incidence of drug-related effects. This reinforces evidence from previous placebo-controlled or head-to-head trials in non-menstrually related migraine, namely that frovatriptan, used for immediate or repeated sustained use, is one of the best tolerated triptans [MacGregor *et al.* 2010; Cady *et al.* 2009; Géraud *et al.* 2002; Kelman *et al.* 2010; Poolsup *et al.* 2005; Wallasch, 2010].

In conclusion, MRM poses a unique set of challenges for the clinician, including the choice of the therapy. Among the variety of effective modalities and strategies available, frovatriptan represents an interesting therapeutic option. Its sustained effect and good tolerability profiles show considerable potential in the acute and prophylactic management of MRM.

Acknowledgements

Special thanks to Stefano Omboni, MD for his collaboration.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

GA has occasionally served as scientific consultant for the manufacturers of frovatriptan.

References

- Allais, G., Acuto, G., Cabarrocas, X., Esbri, R., Benedetto, C. and Bussone, G. (2006) Efficacy and tolerability of almotriptan *versus* zolmitriptan for the acute treatment of menstrual migraine. *Neurol Sci* 27(Suppl. 2): S193–S197.
- Allais, G., Bussone, G., Airola, G., Borgogno, P., Gabellari, I., De Lorenzo, C. *et al.* (2008) Oral contraceptive-induced menstrual migraine. Clinical aspects and response to frovatriptan. *Neurol Sci* 29(Suppl. 1): S186–S190.
- Allais, G., Bussone, G., D'Andrea, G., Moschiano, F., D'Onofrio, F., Valguarnera, F. *et al.* (2011a) Almotriptan 12.5 mg in menstrually related migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 31: 144–151.
- Allais, G., Castagnoli Gabellari, I., De Lorenzo, C., Mana, O. and Benedetto, C. (2007) Menstrual migraine: clinical and therapeutical aspects. *Expert Rev Neurother* 7: 1105–1120.
- Allais, G., Tullo, V., Benedetto, C., Zava, D., Omboni, S. and Bussone, G. (2011b) Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, multicenter, Italian, comparative study *versus* zolmitriptan. *Neurol Sci* 32(Suppl. 1): S99–S104.
- Allais, G., Tullo, V., Omboni, S., Benedetto, C., Sances, G., Zava, D. *et al.* (2012) Efficacy of frovatriptan *versus* other triptans in the acute treatment of menstrual migraine: a pooled analysis of three double-blind, randomized, crossover, multicenter studies. *Neurol Sci* 33(Suppl. 1): S65–S69.
- Balbisi, E. (2006) Frovatriptan: a review of pharmacology, pharmacokinetics and clinical potential in the treatment of menstrual migraine. *Ther Clin Risk Manag* 2: 303–308.
- Bartolini, M., Giamberardino, M., Lisotto, C., Martelletti, P., Moscato, D., Panascia, B. *et al.* (2012) Frovatriptan *versus* almotriptan for acute treatment of menstrual migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study. *J Headache Pain* 13: 401–406.
- Bigal, M., Bordini, C., Antoniazzi, A. and Speciali, J. (2003) The triptan formulations: a critical evaluation. *Arq Neuropsiquiatr* 61: 313–320.
- Brandes, J., Poole, A., Kallela, M., Schreiber, C., MacGregor, E., Silberstein, S. *et al.* (2009) Short-term frovatriptan for the prevention of difficult-to-treat menstrual migraine attacks. *Cephalalgia* 29: 1133–1148.
- Brandes, J., Smith, T., Diamond, M. and Ames, M. (2007) Open-label, long-term tolerability of naratriptan for short-term prevention of menstrually related migraine. *Headache* 47: 886–894.
- Buchan, P., Keywood, C., Wade, A. and Ward, C. (2002) Clinical pharmacokinetics of frovatriptan. *Headache* 42(Suppl. 2): S54–S62.
- Cady, R., Banks, J., Jones, B. and Campbell, J. (2009) Postmarketing migraine survey of frovatriptan: effectiveness and tolerability *versus* previous triptans, NSAIDs or a combination. *Curr Med Res Opin* 25: 2711–2721.
- Comer, M. (2002) Pharmacology of the selective 5-HT(1B/1D) agonist frovatriptan. *Headache* 42(Suppl. 2): S47–S53.
- Cortelli, P., Allais, G., Tullo, V., Benedetto, C., Zava, D., Omboni, S. *et al.* (2011) Frovatriptan *versus* other triptans in the acute treatment of migraine: pooled analysis of three double-blind, randomized, cross-over, multicenter, Italian studies. *Neurol Sci* 32(Suppl. 1): S95–S98.
- Diamond, M., Cady, R., Mao, L., Biondi, D., Finlayson, G., Greenberg, S. *et al.* (2008) Characteristics of migraine attacks and responses to almotriptan treatment: a comparison of menstrually related and nonmenstrually related migraines. *Headache* 48: 248–258.
- Facchinetti, F., Allais, G., Nappi, R., Gabellari, I., Di Renzo, G., Genazzani, A. *et al.* (2010) Sumatriptan (50 mg tablets *versus* 25 mg suppositories) in the acute treatment of menstrually related migraine and oral contraceptive-induced menstrual migraine: a pilot study. *Gynecol Endocrinol* 26: 773–779.
- Ferrari, M., Goadsby, P., Roon, K. and Lipton, R. (2002) Triptans (serotonin, 5-HT_{1B/1D} agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* 22: 633–658.
- Géraud, G., Spierings, E. and Keywood, C. (2002) Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 42(Suppl. 2): S93–S99.
- Guidotti, M., Mauri, M., Barrilà, C., Guidotti, F. and Belloni, C. (2007) Frovatriptan *versus* transdermal oestrogens or naproxen sodium for the prophylaxis of menstrual migraine. *J Headache Pain* 8: 283–288.
- Headache Classification Subcommittee of the International Headache Society (2004) The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* 24(Suppl. 1): 9–160.

- Johnston, M. and Rapoport, A. (2010) Triptans for the management of migraine. *Drugs* 70: 1505–1518.
- Kalra, A. and Elliott, D. (2007) Acute migraine: current treatment and emerging therapies. *Ther Clin Risk Manag* 3: 449–459.
- Kelman, L., Harper, S., Hu, X. and Campbell, J. (2010) Treatment response and tolerability of frovatriptan in patients reporting short- or long-duration migraines at baseline. *Curr Med Res Opin* 26: 2097–2104.
- Landy, S., Savani, N., Shackelford, S., Loftus, J. and Jones, M. (2004) Efficacy and tolerability of sumatriptan tablets administered during the mild-pain phase of menstrually associated migraine. *Int J Clin Pract* 58: 913–919.
- Loder, E. (2010) Triptan therapy in migraine. *N Engl J Med* 363: 63–70.
- Loder, E., Silberstein, S., Abu-Shakra, S., Mueller, L. and Smith, T. (2004) Efficacy and tolerability of oral zolmitriptan in menstrually associated migraine: a randomized, prospective, parallel-group, double-blind, placebo-controlled study. *Headache* 44: 120–130.
- MacGregor, E. (2008) Menstrual migraine. *Curr Opin Neurol* 21: 309–315.
- MacGregor, E. (2010) Prevention and treatment of menstrual migraine. *Drugs* 70: 1799–1818.
- MacGregor, E., Brandes, J., Silberstein, S., Jeka, S., Czapinski, P., Shaw, B. *et al.* (2009) Safety and tolerability of short-term preventive frovatriptan: a combined analysis. *Headache* 49: 1298–1314.
- MacGregor, E., Pawsey, S., Campbell, J. and Hu, X. (2010) Safety and tolerability of frovatriptan in the acute treatment of migraine and prevention of menstrual migraine: results of a new analysis of data from five previously published studies. *Gend Med* 7: 88–108.
- Mannix, L. and Files, J. (2005) The use of triptans in the management of menstrual migraine. *CNS Drugs* 19: 951–972.
- Mannix, L., Savani, N., Landy, S., Valade, D., Shackelford, S., Ames, M. *et al.* (2007) Efficacy and tolerability of naratriptan for short-term prevention of menstrually related migraine: data from two randomized, double-blind, placebo-controlled studies. *Headache* 47: 1037–1049.
- Martin, V., Cady, R., Mauskop, A., Seidman, L., Rodgers, A., Hustad, C. *et al.* (2008) Efficacy of rizatriptan for menstrual migraine in an early intervention model: a prospective subgroup analysis of the rizatriptan TAME (Treat A Migraine Early) studies. *Headache* 48: 226–235.
- Martin, V. and Lipton, R. (2008) Epidemiology and biology of menstrual migraine. *Headache* 48(Suppl. 3): S124–S130.
- Massiou, H., Jamin, C., Hinzelin, G. and Bidaut-Mazel, C.; French Naramig Collaborative Study Group. (2005) Efficacy of oral naratriptan in the treatment of menstrually related migraine. *Eur J Neurol* 12: 774–781.
- Moschiano, F., Allais, G., Grazzi, L., Usai, S., Benedetto, C., D’Amico, D. *et al.* (2005) Naratriptan in the short-term prophylaxis of pure menstrual migraine. *Neurol Sci* 26(Suppl. 2): s162–s166.
- Nett, R., Landy, S., Shackelford, S., Richardson, M., Ames, M. and Lener, M. (2003) Pain-free efficacy after treatment with sumatriptan in the mild pain phase of menstrually associated migraine. *Obstet Gynecol* 102: 835–842.
- Nett, R., Mannix, L., Mueller, L., Rodgers, A., Hustad, C., Skobieranda, F. *et al.* (2008) Rizatriptan efficacy in ICHD-II pure menstrual migraine and menstrually related migraine. *Headache* 48: 1194–1201.
- Newman, L., Harper, S., Jones, B. and Campbell, J. (2009) Frovatriptan for acute treatment of migraine associated with menstruation: results from an open-label postmarketing surveillance study. *J Womens Health (Larchmt)* 18: 1265–1273.
- Newman, L., Lipton, R., Lay, C. and Solomon, S. (1998) A pilot study of oral sumatriptan as intermittent prophylaxis of menstruation-related migraine. *Neurology* 51: 307–309.
- Newman, L., Mannix, L., Landy, S., Silberstein, S., Lipton, R., Putnam, D. *et al.* (2001) Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double-blind, placebo-controlled study. *Headache* 41: 248–256.
- Pascual, J., Mateos, V., Roig, C., Sanchez-Del-Rio, M. and Jiménez, D. (2007) Marketed oral triptans in the acute treatment of migraine: a systematic review on efficacy and tolerability. *Headache* 47: 1152–1168.
- Poolsup, N., Leelasangaluk, V., Jittangtrong, J., Rithlamlert, C., Ratanapantamane, N. and Khanthong, M. (2005) Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. *J Clin Pharm Ther* 30: 521–532.
- Pringsheim, T., Davenport, W. and Dodick, D. (2008) Acute treatment and prevention of menstrually related migraine headache: evidence-based review. *Neurology* 70: 1555–1563.
- Ramadan, N., Skljarevski, V., Phebus, L. and Johnson, K. (2003) 5-HT_{1F} receptor agonists in acute migraine treatment: a hypothesis. *Cephalalgia* 23: 776–785.
- Rapoport, A., Tepper, S., Bigal, M. and Sheftell, F. (2003) The triptan formulations: how to match patients and products. *CNS Drugs* 17: 431–447.

- Savi, L., Omboni, S., Lisotto, C., Zanchin, G., Ferrari, M. and Zava, D. (2011) Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study *versus* rizatriptan. *J Headache Pain* 12: 609–615.
- Schreiber, C. and Cady, R. (2007) Diagnosis of menstrual headache and an open-label study among those with previously undiagnosed menstrually related migraine to evaluate the efficacy of sumatriptan 100 mg. *Clin Ther* 29(Suppl.): 2511–2519.
- Silberstein, S., Berner, T., Tobin, J., Xiang, Q. and Campbell, J. (2009) Scheduled short-term prevention with frovatriptan for migraine occurring exclusively in association with menstruation. *Headache* 49: 1283–1297.
- Silberstein, S., Elkind, A., Schreiber, C. and Keywood, C. (2004) A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology* 63: 261–269.
- Silberstein, S., Holland, S., Freitag, F., Dodick, D., Argoff, C. and Ashman, E. (2012) Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 78: 1337–1345.
- Silberstein, S., Massiou, H., Le Jeunne, C., Johnson-Pratt, L., McCarroll, K. and Lines, C. (2000) Rizatriptan in the treatment of menstrual migraine. *Obstet Gynecol* 96: 237–242.
- Silberstein, S., Massiou, H., McCarroll, K. and Lines, C. (2002) Further evaluation of rizatriptan in menstrual migraine: retrospective analysis of long-term data. *Headache* 42: 917–923.
- Steiner, T., Paemeleire, K., Jensen, R., Valade, D., Savi, L., Lainez, M. *et al.* (2007) European principles of management of common headache disorders in primary care. *J Headache Pain* 8(Suppl. 1): S3–S47.
- Taylor, F. (2009) Clinical aspects of perimenstrual headaches. *Curr Pain Headache Rep* 13: 75–81.
- Tepper, S. (2006) Tailoring management strategies for the patient with menstrual migraine: focus on prevention and treatment. *Headache* 46(Suppl. 2): S61–S68.
- Tuchman, M., Hee, A., Emeribe, U. and Silberstein, S. (2006) Efficacy and tolerability of zolmitriptan oral tablet in the acute treatment of menstrual migraine. *CNS Drugs* 20: 1019–1026.
- Tuchman, M., Hee, A., Emeribe, U. and Silberstein, S. (2008) Oral zolmitriptan in the short-term prevention of menstrual migraine: a randomized, placebo-controlled study. *CNS Drugs* 22: 877–886.
- Wallasch, T. (2010) Frovatriptan in the practice of office-based neurologists/pain therapists: results of postmarketing surveillance study ALADIN. *Adv Ther* 27: 56–62.

Visit SAGE journals online
<http://tan.sagepub.com>

SAGE journals