Treatment strategies for menstrually related migraine

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Approximately 50% of migrainous women suffer from menstrually related migraine (MRM), a type of migraine in which the attacks occur at the same time as or near the menstrual flow. Attacks of MRM tend to be longer, more intense and disabling and sometimes less responsive to treatment than non-menstrual migraines. Similar to the management of non-menstrual migraine, the use of triptans and NSAIDs is the gold standard for MRM treatment. In this paper, the most important studies in the literature that report the effectiveness of triptans, of certain associated drugs and other analgesic agents are summarized. Preventive strategies that can be used if a prophylactic treatment is needed is also analyzed, with particular attention paid to the use of perimenstrual prophylaxis with triptans and/or NSAIDs. Moreover, considering the peculiar interaction between menstrual migraine and female sex hormones, brief mention is made to possible hormonal manipulations.

Migraine is a neurological disorder that predominantly affects the female sex with a female to male ratio of approximately 3:1 [1]. At least 50% of migrainous women have migraine attacks at the same time as or near the menstrual flow [2]. Nonetheless, the prevalence of menstrual migraine (MM) reported in the literature ranges from 4 to 73% [2,3], probably due to a lack of a standard definition of the temporal frame, also defined as the 'perimenstrual period' (PMP), in which the veritable MM attacks must occur.

In 2004, in its guidelines for headache diagnosis (International Classification of Headache Disorders – second edition [ICHD-II]) [4], the International Headache Society recognized (although only in the Appendix) three clinical entities regarding the possible temporal link between migraine and menstruation:

- Pure MM (PMM) without aura (code A1.1.1), in which attacks that meet the criteria for migraine without aura only occur from days -2 to +3 of the menstrual cycle (where day 1 is the first day of menstruation) in at least two out of three menstrual cycles;
- Menstrually related migraine (MRM) without aura (code A1.1.2), in which migraine without aura always occurs on day 1 ± 2 of menstruation in at least two out of three menstrual cycles, and at other times due to different triggering factors or for no apparent specific reason;
- Non-MM (NMM) without aura (code A1.1.3), in which migraine without aura occurs with no menstrual relationship in a menstruating woman.

Since there are decidedly more data available for MRM than for PMM, this review will primarily consider the former.

Clinical aspects

Although opinions differ, most of the data in the literature report that the attacks of MM tend to be longer and more intense than those arising in other phases of the menstrual cycle, and are often aggravated by more pronounced vegetative phenomena (e.g., nausea, vomiting and photo-phonophobia) [5–9]. As a result, the attacks of MM are much more disabling than non-menstrual ones [10]. Considering the particular clinical picture that characterizes MM, it is not surprising that the attacks often prove to be difficult to treat as well.

Treatment strategies

The first step is always to identify drugs for the acute attack that are also effective in treating the more severe and disabling attacks of MM. If such attacks are particularly refractory to the symptomatic drug, one can resort to a prophylactic treatment designed to reduce the frequency, intensity and duration of the attacks.

Acute treatment options

A pivotal meta-analysis on the use of triptans as acute migraine treatment showed that these selective 5-hydroxytryptamine 1B/1D-receptor agonists are highly effective and well tolerated, albeit with some differences among them as demonstrated by numerous clinical trials [11,12]. Although the pathophysiology of MM and NMM may partially differ, the acute treatments

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typically recommended are the same for both conditions. Therefore, the drugs of choice for acute attacks of MM are triptans. Other treatment options include various analgesics and anti-emetic agents, NSAIDs, COX-2 inhibitors and ergot derivatives. More recently, associated drugs, such as sumatriptan plus naproxen and rizatriptan plus dexamethasone, have been tested in the specific treatment of MM.

With regards to triptans, in the discussion, prospective, randomized controlled studies (RCTs) will only be taken into account, with particular attention to the 2 and 24-h pain-free response when available. These are considered the meaningful outcomes from the patient's perspective. In older trials evaluating acute antimigraine drugs, the outcome traditionally used was 2-h pain relief (defined as a decrease from moderate or severe pain to mild or no pain). However, more recently, 2-h pain free (decrease from moderate or severe pain to no pain) and sustained pain free (pain free at 2-h with no recurrence of moderate-to-severe headache and no use of rescue medication from 2 to 24-h after dose) have been recommended as the preferred end points [12,13]. This choice means that success percentages will seem lower than those obtained with the previous end point, but as indicated by some surveys, sufferers consider complete pain relief, no recurrence and rapid onset to be the most important attributes of their acute treatment [14].

Triptans

In many retrospective and prospective studies, triptans have proven to be effective for acute treatment of both MM and NMM. Results from RCTs on the use of triptans in MM treatment are summarized in Table 1, with particular attention paid to the pain-relief and pain-free end point. Furthermore, for some triptans (i.e., sumatriptan, zolmitriptan, rizatriptan, naratriptan and almotriptan), there are data suggesting that they are also effective in significantly reducing associated symptoms, such as nausea, vomiting and photo-phonophobia.

Sumatriptan

Sumatriptan has been proven to be a highly effective and tolerable treatment of MM. The first formulation tested was subcutaneous 6 mg sumatriptan, which was assessed in the treatment of one or two attacks of MRM [15]. In the first attack, after sumatriptan injection, 73% of patients obtained 2-h pain relief and 55% were pain free, whereas in the placebo group only 31 and 14%, respectively, achieved pain relief or a pain-free condition ($p < 0.001$). Similar results were also obtained for the second attack.

With regards to sumatriptan tablets, the efficacy of the 100 mg dosage for the treatment of MRM compared with NMM attacks was assessed in two RCTs [16,17]. Results showed a similar efficacy of sumatriptan for both types of migraine, and in both cases it was superior to placebo. For results at different end points see Table 1.

Since it has been demonstrated that early intervention (i.e., treatment of a migraine attack while pain is still mild rather than delaying treatment until pain has progressed to moderate or severe) may be a useful approach, especially in the case of difficult-to-treat migraine, the efficacy and tolerability of two different dosages of sumatriptan (50 and 100 mg) administered in the mild-pain phase of MRM was evaluated in two RCTs [18,19]. A 2-h pain-free response was present in more than 50% of the sumatriptan-treated patients and both dosages were significantly more effective when compared with placebo. Moreover, freedom from pain at 2 h was achieved by a greater percentage of patients who had treated the attack immediately during the mild phase, compared with the global sample that had treated the attack at any degree of severity.

The combination of 85 mg sumatriptan and 500 mg naproxen sodium in a single tablet was proposed in order to potentiate the therapeutic effect in the case of MRM. The efficacy and tolerability of this combination drug was evaluated in two RCTs for a total of 621 women suffering from MRM in association with dysmenorrhea [20]. The rate of 2 and 24-h sustained pain-free response was statistically higher for sumatriptan–naproxen compared with placebo, and women taking sumatriptan–naproxen continued to be pain free for 48 h. Moreover, this combination drug also relieved nonpainful menstrual symptoms such as bloating, tiredness and irritability.

Finally, a crossover, randomized trial was performed to evaluate the efficacy and safety of rectal (25 mg) and oral (50 mg) sumatriptan for the treatment of MRM and of the so-called 'oral contraceptive-induced MM' [21]. This latter subtype of migraine fulfils the ICHD-II criteria for the 'estrogen-withdrawal headache' (code 8.4.3), and was described in the study as a migraine that arose in the days when oral contraceptive was suspended.

Results showed that in the MRM group, a 2-h pain-free response was reached by 24 and 27%

of patients, respectively, after the use of suppository and oral tablets; in the oral contraceptive-induced MM group, 27 and 18% of patients, respectively, were pain free after suppository and oral-tablet use.

Zolmitriptan

The efficacy of zolmitriptan as acute treatment of MRM has been assessed in a study in which the drug dosage was chosen based on migraine intensity: patients were instructed to take half

Table 1. Published randomized trials on triptans in the acute treatment of menstrual migraine.

End point	Study	Intervention	Responder rate (%)	Significance (p-values)	Ref.
1-h pain relief	Facchinetti *et al.*	Sumatriptan 6 mg vs placebo			[15]
		Attack 1 (n = 179)	71 vs 22	<0.001	
		Attack 2 (n = 139)	70 vs 24	<0.001	
	Loder *et al.*	Zolmitriptan 1.25/2.5/5 mg vs placebo (n = 510)†	33 vs 23	<0.0001	[22]
	Tuchman *et al.*	Zolmitriptan 2.5 mg vs placebo (n = 334)	40.6 vs 22.3	<0.0001	[23]
	Allais *et al.*	Almotriptan 12.5 mg vs zolmitriptan 2.5 mg (n = 255)	30.6 vs 33.9	NS	[31]
2-h pain relief	Facchinetti *et al.*	Sumatriptan 6 mg vs placebo			[15]
		Attack 1 (n = 179)	73 vs 31	<0.001	
		Attack 2 (n = 139)	81 vs 29	<0.001	
	Mannix *et al.*	Rizatriptan 10 mg vs placebo			[24]
		Study 1 (n = 357)	70 vs 53	0.001	
		Study 2 (n = 350)	73 vs 50	<0.001	
	Nett *et al.*	Rizatriptan 10 mg vs placebo			[26]
		PMM (n = 146)	73 vs 50	0.006	
		MRM (n = 561)	71 vs 52	<0.001	
	Loder *et al.*	Zolmitriptan 1.25/2.5/5 mg vs placebo (n = 510)†	48 vs 27	<0.0001	[22]
	Tuchman *et al.*	Zolmitriptan 2.5 mg vs placebo (n = 334)	65.7 vs 32.8	<0.0001	[23]
	Allais *et al.*	Frovatriptan 2.5 mg vs zolmitriptan 2.5 mg (n = 138)	52 vs 53	NS	[29]
	Savi *et al.*	Frovatriptan 2.5 mg vs rizatriptan 10 mg (n = 108)	58 vs 64	NS	[30]
	Allais *et al.*	Almotriptan 12.5 mg vs zolmitriptan 2.5 mg (n = 255)	67.9 vs 68.6	NS	[31]
	Diamond *et al.*	Almotriptan 12.5 mg MRM vs NMM (n = 42)	77.4 vs 68.3	NS	[32]
4-h pain relief	Gross *et al.*	Sumatriptan 100 mg vs placebo (n = 97)	67 vs 33	NA	[16]
	Tuchman *et al.*	Zolmitriptan 2.5 mg vs placebo (n = 334)	81.7 vs 57.9	<0.0001	[23]
24-h sustained pain relief	Mannix *et al.*	Rizatriptan 10 mg vs placebo			[24]
		Study 1 (n = 357)	46 vs 33	0.016	
		Study 2 (n = 350)	46 vs 33	0.024	
	Nett *et al.*	Rizatriptan 10 mg vs placebo			[26]
		PMM (n = 146)	42 vs 36	‡	
		MRM (n = 561)	47 vs 32	‡	
	Allais *et al.*	Frovatriptan 2.5 mg vs zolmitriptan 2.5 mg (n = 138)	83 vs 82	NS	[29]
	Savi *et al.*	Frovatriptan 2.5 mg vs rizatriptan 10 mg (n = 108)	81 vs 74	NS	[30]

Pain relief: reduction from moderate or severe pain to mild or no pain.
Sustained pain relief: maintenance of pain relief for at least 24 h after drug intake.
Pain free: absence of pain.
Sustained pain free: absence of pain after 2 h with no recurrence of moderate or severe pain and no use of a second dose of study medication or rescue medications during the 24 h after treatment.
†See text for more details.
‡Authors stated that statistical testing was not perfomed.
§Results relative to treatment of attacks in mild pain phase.
MRM: Menstrually related migraine; NA: Not applicable (authors did not provide the p-value); NMM: Non-menstrual migraine; NS: Not significant; PMM: Pure menstrual migraine.

Table 1. Published randomized trials on triptans in the acute treatment of menstrual migraine (cont.).

End point	Study	Intervention	Responder rate (%)	Significance (p-values)	Ref.
1-h pain free	Facchinetti *et al.*	Sumatriptan 6 mg vs placebo			[15]
		Attack 1 (n = 179)	33 vs 10	<0.001	
		Attack 2 (n = 139)	Similar to attack 1	<0.001	
	Tuchman *et al.*	Zolmitriptan 2.5 mg vs placebo (n = 334)	6.2 vs 2.5	0.005	[23]
	Nett *et al.*	Sumatriptan 100 mg vs placebo (n = 115)§	30 vs 14	0.006	[18]
		Sumatriptan 50 mg (n = 116)§	25 vs 14	0.052	
	Loder *et al.*	Zolmitriptan 1.25/2.5/5 mg vs placebo (n = 510)†	10 vs 6	0.03	[22]
	Allais *et al.*	Almotriptan 12.5 mg vs zolmitriptan 2.5 mg (n = 255)	8.1 vs 8.4	NS	[31]
2-h pain free	Facchinetti *et al.*	Sumatriptan 6 mg vs placebo			[15]
		Attack 1 (n = 179)	55 vs 14	<0.001	
		Attack 2 (n = 139)	Similar to attack 1	<0.001	
	Nett *et al.*	Sumatriptan 100 mg vs placebo (n = 115)§	61 vs 29	<0.001	[18]
		Sumatriptan 50 mg (n = 116)§	51 vs 29	<0.001	
	Landy *et al.*	Sumatriptan 100 mg vs placebo (n = 248)§			[19]
		Study 1	58 vs 22	<0.001	
		Study 2	61 vs 29	<0.001	
		Sumatriptan 50 mg vs placebo (n = 254)§			
		Study 1	51 vs 22	<0.001	
		Study 2	51 vs 29	<0.001	
	Martin *et al.*	Rizatriptan 10 mg vs placebo (n = 94)§	63.5 vs 29	0.002	[25]
	Nett *et al.*	Rizatriptan 10 mg vs placebo			[26]
		PMM (n = 146)	42 vs 12	‡	
		MRM (n = 561)	36 vs 19	‡	
	Loder *et al.*	Zolmitriptan 1.25/2.5/5 mg vs placebo (n = 510)†	26 vs 10	<0.0001	[22]
	Tuchman *et al.*	Zolmitriptan 2.5 mg vs placebo (n = 334)	27.5 vs 9.2	<0.0001	[23]
	Massiou *et al.*	Naratriptan 2.5 mg vs placebo (n = 229)	43 vs 25	0.004	[28]
	Allais *et al.*	Frovatriptan 2.5 mg vs zolmitriptan 2.5 mg (n = 138)	22 vs 26	NS	[29]
	Savi *et al.*	Frovatriptan 2.5 mg vs rizatriptan 10 mg (n = 108)	31 vs 34	NS	[30]
	Allais *et al.*	Almotriptan 12.5 mg vs zolmitriptan 2.5 mg (n = 255)	44.9 vs 41.2	NS	[31]
	Diamond *et al.*	Almotriptan 12.5 mg MRM vs NMM (n = 42)	35.4 vs 35.9	NS	[32]
	Allais *et al.*	Almotriptan 12.5 mg vs placebo (n = 147)	48.4 vs 26.2	0.0008	[33]
4-h pain free	Massiou *et al.*	Naratriptan 2.5 mg vs placebo (n = 229)	58 vs 30	<0.001	[28]
	Tuchman *et al.*	Zolmitriptan 2.5 mg vs placebo (n = 334)	51.6 vs 25.3	<0.0001	[23]

Pain relief: reduction from moderate or severe pain to mild or no pain.
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Pain free: absence of pain.
Sustained pain free: absence of pain after 2 h with no recurrence of moderate or severe pain and no use of a second dose of study medication or rescue medications during the 24 h after treatment.
†See text for more details.
‡Authors stated that statistical testing was not perfomed.
§Results relative to treatment of attacks in mild pain phase.
MRM: Menstrually related migraine; NA: Not applicable (authors did not provide the p-value); NMM: Non-menstrual migraine; NS: Not significant; PMM: Pure menstrual migraine.

Table 1. Published randomized trials on triptans in the acute treatment of menstrual migraine (cont.).

End point	Study	Intervention	Responder rate (%)	Significance (p-values)	Ref.
24-h sustained pain free	Nett *et al.*	Sumatriptan 100 mg vs placebo (n = 115)§	31 vs 14	0.004	[18]
		Sumatriptan 50 mg vs placebo (n = 116)§	30 vs 14	0.007	
	Landy *et al.*	Sumatriptan 100 mg vs placebo (n = 248)§			[19]
		Study 1	73 vs 27	<0.001	
		Study 2	65 vs 23	<0.001	
		Sumatriptan 50 mg vs placebo (n = 254)§			
		Study 1	62 vs 27	<0.001	
		Study 2	55 vs 23	0.012	
	Martin *et al.*	Rizatriptan 10 mg vs placebo (n = 94)§	41.3 vs 25.8	0.079	[25]
	Nett *et al.*	Rizatriptan 10 mg vs placebo			[26]
		PMM (n = 146)	23 vs 10	‡	
		MRM (n = 561)	24 vs 14	‡	
	Massiou *et al.*	Naratriptan 2.5 mg vs placebo (n = 229)	42 vs 20	<0.001	[28]
	Allais *et al.*	Frovatriptan 2.5 mg vs zolmitriptan 2.5 mg (n = 138)	74 vs 69	NS	[29]
	Savi *et al.*	Frovatriptan 2.5 mg vs rizatriptan 10 mg (n = 108)	67 vs 61	NS	[30]
	Allais *et al.*	Almotriptan 12.5 mg vs zolmitriptan 2.5 mg (n = 255)	29.3 vs 27.1	NS	[31]
	Diamond *et al.*	Almotriptan 12.5 mg MRM vs NMM (n = 42)	22.9 vs 23.8	NS	[32]
	Allais *et al.*	Almotriptan 12.5 mg vs placebo (n = 147)	36.1 vs 17.2	0.0022	[33]

Pain relief: reduction from moderate or severe pain to mild or no pain.
Sustained pain relief: maintenance of pain relief for at least 24 h after drug intake.
Pain free: absence of pain.
Sustained pain free: absence of pain after 2 h with no recurrence of moderate or severe pain and no use of a second dose of study medication or rescue medications during the 24 h after treatment.
†See text for more details.
‡Authors stated that statistical testing was not perfomed.
§Results relative to treatment of attacks in mild pain phase.
MRM: Menstrually related migraine; NA: Not applicable (authors did not provide the p-value); NMM: Non-menstrual migraine; NS: Not significant; PMM: Pure menstrual migraine.

of a 2.5 mg zolmitriptan tablet (or placebo) in case of mild attacks; 2.5 mg zolmitriptan (or placebo) in case of moderate attacks; and 5 mg zolmitriptan (or placebo) in case of severe attacks [22]. Zolmitriptan showed significant superiority to placebo in achieving a pain-free response at 30 min, 1 and 2 h after dosing, regardless of the intensity of the attack. A recent study showed similar results in terms of a 2-h pain-free rate with the use of 2.5 mg zolmitriptan compared with placebo [23]. For more details see Table 1.

Rizatriptan

The first prospective RCTs have only been available since 2007, despite the fact that retrospective data analyses on the use of rizatriptan in treating MM were already present in the literature. The first data was derived from two prospective RCTs on patients suffering from MRM [24]. Rizatriptan at 10 mg was shown to be significantly better than placebo in achieving 2-h pain relief and 24-h sustained pain relief.

A subgroup analysis of the rizatriptan TAME study provided data relative to the use of 10 mg rizatriptan in the early treatment of MRM attacks; patients were instructed to take the study medication within 1 h of migraine onset and when the pain was mild. A 2-h pain-free response was significantly higher in the rizatriptan group compared with the placebo group [25].

Rizatriptan was also specifically tested for the treatment of PMM as compared with treatment of MRM [26]. As reported in Table 1, 10 mg rizatriptan was similarly effective for both PMM and MRM.

Finally, the efficacy of associating 10 mg rizatriptan with 4 mg dexamethasone was tested in the treatment of MRM [27]. In a randomized, double-blind, crossover study in which 35 patients treated a total of 190 attacks of MRM with, respectively, 10 mg rizatriptan, 4 mg dexamethasone and the association of both (two attacks each). The pain-free rate at 2 h was

50.8 versus 19.7%, respectively, for rizatriptan versus dexamethasone ($p < 0.01$), while the association of rizatriptan plus dexamethasone was not significantly different from rizatriptan alone. Also the 24-h pain-free response was higher for rizatriptan compared with dexamethasone (respectively, 32.2 vs 12.1%; $p < 0.05$); and the combination of rizatriptan plus dexamethasone was superior to both rizatriptan (50.7 vs 32.2%; $p < 0.05$) and dexamethasone (50.7 vs 12.1%; $p < 0.001$) for this end point. However, the combination of rizatriptan plus dexamethasone was associated with a higher rate of adverse events.

Naratriptan

Only one study tested the use of naratriptan for the specific treatment of MRM [28]. In this trial, patients were instructed to treat a single MRM attack with 2.5 mg naratriptan or placebo. Naratriptan was better than placebo in achieving both a 2-h pain-free response and a sustained pain-free response from 4 to 24 h ($p < 0.001$). For detailed results see Table 1.

Frovatriptan

Specific RCTs have not as yet been conducted on the use of frovatriptan for the treatment of MRM, although two subgroup analyses are present in the recent literature. Both are RCTs with a crossover design in which 2.5 mg frovatriptan is compared with 2.5 mg zolmitriptan [29] and rizatriptan [30]. No significant differences were present between frovatriptan and the two other triptans concerning pain-free rate at 2 and 24 h. However, recurrence at 24 h was significantly lower for frovatriptan.

Almotriptan

Two *post-hoc* analyses have already demonstrated the efficacy of almotriptan in the treatment of MRM [31,32], although the first prospective RCT was only published in 2011 [33]. In this study on MRM sufferers, almotriptan showed its superiority compared with placebo in reaching a 2 and 24-h pain-free condition. Results are summarized in Table 1.

Eletriptan

There are also no prospective RCTs in the literature for eletriptan and only one retrospective analysis of six trials is available [34]. Both dosages of eletriptan (40 and 80 mg) were effective in treating MRM, although the end point was only an undefined 'headache response' at 2 h (64% for 40 mg eletriptan, 68% for 80 mg eletriptan, 26% for placebo; $p < 0.001$).

Analgesic agents

The efficacy of a combination of 500 mg acetaminophen, 500 mg aspirin and 130 mg caffeine for the treatment of MRM compared with NMM was evaluated in a *post-hoc* analysis of pooled data from three RCTs. The combination drug was more effective than placebo at all postdose time points ($p \leq 0.05$). Moreover, there was no statistically significant difference in treatment effect between MRM and NMM [35].

With a crossover design, 500 mg mefenamic acid was compared with placebo for the treatment of MRM [36]. Women were instructed to take the drug when a headache started and to repeat the intake every 8 h throughout menses (total dose of mefenamic acid: 1500 mg/24 h). Results showed that mefenamic acid was significantly superior to placebo in achieving a pain-relief response.

Prophylactic treatment options

Perimenstrual attacks are characterized by a predictable nature, thus they can be considered as candidates for intermittent prophylaxis, which cover the whole period of susceptibility. A prophylactic treatment around the PMP is feasible provided that three conditions can be verified: that the frequency of non-menstrual attacks is low; that the menstrual cycle is regular enough; and that the attack occurs at a time sufficiently precise compared with the beginning of the menstrual flow. Predictability is an essential prerequisite.

Various treatment options are available based on the regularity of the menstrual cycles, the time of onset of the attacks relative to the beginning of the menstrual flow, the possible presence of dysmenorrhea or the need for contraception. The agents most commonly used as supplementations during PMP include NSAIDs, triptans and estradiol.

If the menstrual attacks are not perfectly predictable, one can resort to a supplementation with natural products, such as phytoestrogens or magnesium, administered for a longer perimenstrual interval, sometimes starting from ovulation.

Another possible strategy is to suppress the menstrual cycle entirely. However, the drugs utilized, such as danazol, tamoxifene, and gonadotropin-releasing hormone agonists, were tested for this purpose only in trials with very low numbers. Moreover, they tend to generate significant side effects and must be reserved for highly selected cases [37].

Finally, this article will also consider the treatment options that may be used in the particular case of 'estrogen-withdrawal headache' (i.e., the

particular type of MM that actually occurs during the period when hormonal contraceptives are suspended).

Short-term prophylaxis

Before prescribing any prophylactic therapy, it is extremely useful if the patient fills in a diary card of headaches for a few months, with particular attention to the PMP episodes to determine whether or not the presumed menstrual attacks are actually predictable enough, as previously mentioned. Nevertheless, there is no agreement on which is the best time of administration: at the expected onset of menstruation or at the expected onset of headache.

NSAIDs

NSAIDs are usually recommended not only because of their efficacy, but also because they are able to prevent other forms of perimenstrual pain such as dysmenorrhea.

The use of naproxen sodium (550 mg two-times/day) from day -7 to day +6 was significantly effective in reducing headache frequency, duration and intensity, as well as the use of escape medications when compared with placebo [38]. In the second and third month of naproxen sodium intake, 33% of patients reported absence of migraine, whereas none of the patients were headache free in the placebo group. Furthermore, the use of granular nimesulide at the dosage of 100 mg three-times/day (for 10 days starting at the onset of migraine) significantly reduced the duration and intensity of migraine compared with placebo ($p = 0.0001$) [39]. Finally, fenoprofen calcium (600 mg two-times/day, from day -3 and continued throughout menses), has proven to be effective in MM prophylaxis [40].

Nonetheless, NSAIDs can lead to gastrointestinal irritation. In the event that the common anti-inflammatory drugs are not well tolerated, COX-2 inhibitors can be used, a class of selective COX-2 inhibitors characterized by lower gastrointestinal toxicity. Their efficacy in the prevention of MRM has only been demonstrated in an open-label pilot study on 20 patients. The administration of 200 mg/day celecoxib or 25 mg/day rofecoxib (from day -2 to day +7) was able to significantly reduce the number of days with MRM (from 4 to 1.8), the number of MRM attacks (from 2.1 to 1.1) and the number of rescue medications (from 5.3 to 2.9) compared with pretreatment measures [41]. However, rofecoxib has been withdrawn because of concerns about cardiovascular safety with long-term use at high dosages.

Triptans

Triptans are currently prescribed for the treatment of acute attacks. However, five of the seven triptans available on the market have also been tested as short-term MM prophylaxis, even though this remains an off-label prescription.

Sumatriptan

The first triptan tested for MM prophylaxis in an open-label study was sumatriptan. Patients were asked to take 25 mg sumatriptan three-times/day for 5 days, starting 3 days before the expected onset of migraine. At the end of the sixth cycle of treatment, migraine disappeared in 52.4% of patients and migraine severity was halved in 42% of the attacks [42].

Naratriptan

The use of 1 mg naratriptan two-times/day, from 2 days before to 3 days after the expected onset of menses, was able to significantly reduce migraine frequency ($p < 0.05$) after four PMPs and number of days with MM ($p < 0.01$) compared with placebo. Moreover, MM disappeared in a higher percentage of patients treated with the active drug than with placebo ($p = 0.003$) [43]. The same dosage of naratriptan, administered for 6 days starting 2 days before the expected onset of menstruation, was also tested in the specific case of PMM [44]. At the end of the third month of treatment, the mean number of PMM attacks decreased from 3.5 to 1.3 and 61.4% of patients experienced a ≥50% decrease in the mean number of attacks. The severity and associated symptoms also tended to decrease during the treatment.

The last published study reports data from two RCTs [45]. In these trials women were instructed to take 1 mg naratriptan two-times/day in the same PMP described above. The percentages of PMPs without MRM was higher in the active drug group compared with placebo (study 1: 38 vs 29%; study 2: 34 vs 23%; $p < 0.005$ for both).

Frovatriptan

The use of frovatriptan as a prophylaxis of MM seems to be promising because of its long half-life, which makes it particularly suitable for the treatment of attacks that often prove to be longer than non-menstrual ones.

The efficacy of frovatriptan taken as MM prophylaxis for 6 days, starting 2 days before the expected onset of menses, was compared with placebo [46]. In the group of 2.5 mg/day frovatriptan once/day, the rate of MM attacks was 52%, decreasing to 41% when frovatriptan

was taken two-times/day. Both frovatriptan regimens were significantly superior to placebo in decreasing not only the frequency of MM attacks ($p < 0.0001$), but also the severity ($p < 0.0001$), duration ($p < 0.0001$) and use of escape medications in a dose-dependent manner.

A subsequent study on women with documented difficult-to-treat MRM tested the efficacy of 2.5 mg frovatriptan once or two-times/day (with a double dose on the first day of treatment in both groups) as a prophylaxis in the same PMP described above [47]. The mean number of PMPs without headache was significantly higher for both frovatriptan dosages compared with placebo: 0.92 for frovatriptan two-times/day ($p < 0.001$), 0.69 for frovatriptan once/day ($p < 0.02$) and 0.42 for placebo.

Zolmitriptan

Zolmitriptan has been tested as a prophylaxis for MRM in only one RCT [48]. Two hundred and forty four patients were randomized to use 2.5 mg zolmitriptan three-times or two-times/day, or placebo three-times/day for three consecutive menstrual cycles for 7 days, starting 2 days before the expected onset of menses. Both zolmitriptan regimens demonstrated superior efficacy compared with placebo, as measured by the proportion of patients with a reduction of ≥50% in the frequency of MRM attacks (placebo three-times/day [37.8%]; zolmitriptan three-times/day [58.6%; $p = 0.0007$] vs placebo; zolmitriptan two-times/day [54.7%; $p = 0.002$] vs placebo).

Eletriptan

Only one open-label study on eletriptan is present in the literature [49]. Sixty one women with MRM were instructed to take 20 mg eletriptan three-times/day from 2 days before to 4 days after the expected onset of menstruation. The mean number of headache days during the PMPs significantly decreased from 8.7 to 4.9 days at the end of the third month of eletriptan treatment ($p = 0.008$).

Ergot derivatives

With regards to this option, no RCTs and only open-label studies with limited number of cases are present in the literature.

The administration of 10 mg/day dihydroergotamine in a slow-release formulation from the 23rd day of a menstrual cycle to the sixth day after the onset of menstruation, was able to significantly reduce the Pain Total Index (a composite measure constituted by the duration in hours × severity of migraine) in the first month (from 199.8 to 25.3; $p < 0.001$) and in the subsequent 3 months ($p < 0.01$) [50]. It has been shown that administration for a shorter time (starting only 2 days before the expected onset of menses) of a slow-release formulation of dihydroergotamine two-times/day for 5 months was also able to significantly reduce the headache index score compared with pretreatment measurement (28.0 vs 69.1; $p < 0.001$), as well as headache duration (17.18 vs 28.56 h; $p < 0.01$) [51].

In another open-label study, 0.2 mg of ergonovine four-times/day, starting from 1 day before to 1 day after the onset of menses, significantly reduced headache severity in 60% of patients, reduced the number of attacks in 15% and was ineffective in 35% [52].

Hormone manipulations of estradiol fluctuations

It is believed that one of the principal triggers of MM attacks is the reduction in the level of estrogen during the late luteal phase of the ovarian cycle after prolonged exposure to elevated levels of these hormones [9,53]. Therefore, attacks may be prevented by reducing or eliminating the estrogen withdrawal [9,54], which could be achieved mainly by increasing the estrogen levels during the PMP when endogenous production is physiologically low. The best route of delivery of estrogen seems to be the gel and patches since they secure the most stable blood steroid levels, avoiding either the brief daily fluctuations associated with oral administration or the initial supra-physiological increase typical of the injectable formulation [55].

Percutaneous estradiol gel

In women suffering from PMM, the administration of 1.5 mg estradiol for a total of 9 days, starting 2 days before menses, was associated with a significant reduction in the frequency, duration and severity of PMM attacks. In the estradiol group, attacks were present in only 30.8% of patients (vs 93.3% of those using placebo), the difference in response to treatment was highly significant ($p < 0.01$ for the comparison between the first and second cycles, $p < 0.001$ for the comparison between the second and third cycles). Moreover, attacks were considerably milder and shorter [56]. In another randomized, controlled, crossover study, percutaneous estradiol gel administered for a total of 7 days, starting at least 2 days prior to the onset of menses, was able to significantly reduce the frequency of MM ($p < 0.001$) compared with placebo [57].

Twenty years later, in a double-blind, 3-month, crossover trial, a longer daily administration of 1.5 mg estradiol gel was tested starting the day after ovulation and continuing until the second day of menses. Active treatment was able to significantly reduce migraine days (relative risk: 0.78; 95% CI: 0.62–0.99; p = 0.03) and the severity of the attacks (p = 0.03). However, in the 5 days following estradiol use, migraine frequency tended to increase compared with placebo (relative risk: 1.40; 95% CI: 1.03–1.92; p = 0.03). In conclusion, it seems that the benefit achieved by perimenstrual estradiol supplementation was offset by postphoned estrogen withdrawal, which triggered migraine immediately after the treatment [58].

Transdermal estradiol patches

Placebo-controlled studies on the use of transdermal estradiol patches have shown conflicting results.

In two double-blind trials, transdermal therapeutic system (TTS) 50, containing 3.2 mg micronized estradiol, was shown to be no more effective than placebo, probably due to inadequate dosage [59,60]. In another trial, MM was prevented with TTS 100 containing 6.4 mg estradiol, but not TTS 25 containing 1.6 mg estradiol [61]. Nevertheless, these results were not confirmed in a recent study, in which the use of estradiol patches with 7.6 mg of estradiol showed no significant difference in efficacy compared with the placebo [62].

Natural products

Phytoestrogens

Phytoestrogens are estrogen-like molecules derived from soy that exert estrogenic activity in a limited number of estrogen-target tissues (mainly in the endothelium, brain, bone, intestinal mucosa, kidney, lung parenchyma and bone marrow), but not on the endometrium. This selectivity theoretically confers greater long-term safety than estradiol supplementation, although this has not yet been clearly confirmed.

One RCT evaluated the efficacy of a combination of 75 mg soy extract standardized to 40% isoflavones, 50 mg dong-quai extract standardized to 1% ligustilide and 25 mg black-cohosh extract standardized to 8% triterpenes, used two-times/day for 24 weeks to prevent MRM [63]. Compared with the placebo group (p < 0.01), the mean frequency of MMs was reduced in the phytoestrogen group.

In addition, in a small, open-label trial, there was a decrease in the number of migraine days after 3 months (p < 0.005) with the administration of a daily dose of 56 mg genistein associated with 20 mg diadzein, only during the PMP (from day -7 to day +3) [64].

Magnesium

Magnesium (Mg^{2+}) is an essential element involved in plasma membrane stability and able to modulate neuronal excitability and vascular tone. Its efficacy as a prophylactic agent in MRM has been tested in a RCT [65]. Both the administration of 360 mg/day of Mg^{2+} pyrrolidone carboxylic acid or placebo from the 15th day of the cycle until the next menses was able to decrease the Pain Total Index of headache. Patients in the Mg^{2+} group, however, reached significantly lower values (p < 0.03) and fewer headache days (p < 0.01). In addition, Mg^{2+} intake also improved premenstrual complaints.

Estrogen-withdrawal headache

As previously described, in some women using combined hormonal contraceptives, a MM attack can appear during the hormone-free interval (HFI) [66,67]. This type of migraine has recently been codified by the ICHD-II as an 'estrogen-withdrawal headache' [4]. In order to prevent the fall of estrogen levels, it is possible to eliminate the HFI by using a continuous regimen (i.e., continuous use of a combined contraceptive or progestogen-only contraceptive). Another option is to simply reduce the magnitude of the estrogen fall by shortening the HFI to less than the usual 7 days or by using low-dose estrogen supplementation in the pill-free week [68].

Elimination of the HFI

Extended regimen of combined oral contraceptives

Numerous studies have confirmed the hypothesis that compared with standard regimens, extended regimens of combined oral contraceptive (COC) are effective in reducing headache as a withdrawal symptom [69–74]. Today, different formulations are offered on the market and their clinical impact and safety have been tested in many trials [70]. However, these are off-label prescriptions and the impact that continuous use of COCs may have on headache has been investigated in only one prospective cohort study [71]. In this trial, 102 women were asked to use a pill containing 3 mg drospirenone/0.03 mg ethinylestradiol (EE) for two cycles of the standard 21/7-day regimen (21 days of active pill intake, followed by 7 days of pill suspension). Thereafter, women had to take the

same formulation continuously for 168 days. Compared with the standard regimen, the continuous use of COC was able to reduce the headache severity significantly ($p < 0.0001$) throughout the 168-day extended regimen, thus leading to an improvement in the quality of life and in work productivity ($p = 0.004$). Unfortunately, this study did not focus specifically on migraine but on a more general headache condition.

Progestogen-only contraceptives

In migrainous women that refuse continuous regimens of COCs, in those that did not tolerate COCs because of side effects related to their estrogenic component, or in those who present contraindications to COCs, a progestogen-only pill (POP) could be a valid alternative for MM prophylaxis.

The first randomized study on this topic compared the continuous intake of a POP containing 75 µg desogestrel (DSG) once/day for 6 months, with an extended regimen of COC containing 150 µg DSG and 30 µg EE. Results demonstrated that both treatments were able to significantly reduce migraine frequency ($p < 0.001$) and the mean duration and intensity of the attacks ($p < 0.001$), with a greater reduction in the POP group [75].

POPs are also useful in patients suffering from migraine with aura (MA) in whom the use of COCs is contraindicated [76]. A recent prospective, open-label study has been performed on 30 women with MA: half of them had previously used COCs, while 15 had never used them [77]. The continuous use of 75 µg DSG once/day throughout 6 months was able to decrease the migraine frequency in both groups (respectively, $p < 0.001$ and $p < 0.02$) Interestingly, the POP was also able to reduce the duration of the aura symptoms, achieving a statistical significance in women in whom MA onset was related to previous COC use.

Reduction of the estrogen fall

COCs supplemented with estrogens

No controlled trials are available on this topic. An open-label study tested the use of 0.9 mg conjugated equine estrogens (i.e., 10 µg of synthetic EE) during the pill-free week of a standard 21-day regimen with oral contraceptive containing 20 µg (EE) as supplementation for MM prophylaxis. Estrogen supplementation conferred a 76% decrease in the mean number of headache days per month and a 77.9% reduction in the headache intensity score [78].

COCs with reduced HFI

Instead of the usual 21/7-day oral contraceptive regimen, there are new monophasic COCs containing 24 active pills (followed by 4 days of placebo pills) and some multiphasic formulations with 22–26 active pills (followed by 6–2 placebo pills). The rationale for using this regimen in MM prophylaxis lies in greater ovarian suppression, which carries lower fluctuations of endogenous estradiol [79,80]. Although no studies have evaluated the impact of these formulations on headache, women generally report good tolerability of these pills [81].

Future perspective

An initial step towards a better understanding and management of MM must come from its inclusion in the final version of the ICHD-III of the International Headache Society, which will probably come out in January 2013. The acquisition of standardized criteria for the definition will permit a comparison and clear interpretation of individual trials and studies.

As for acute treatment, considering the marked role played by prostaglandins in the pathogenesis of the MM attack [82], it is likely that new associations of triptan plus NSAIDs will appear on the market along with the currently available ones based on sumatriptan and naproxen sodium. The use of these combination products can be particularly helpful to those women who develop the MM attack in the first two days of menstrual flow and simultaneously suffer from dysmenorrhea.

From the perspective of preventing the onset of the attack, instead, more widespread use of continuous regimens of COC will probably make effective MM prophylaxis more practicable in patients who take oral contraceptives. As for other disorders, such as severe dysmenorrhea or endometriosis, one may also hope that this indication will appear on the illustrated leaflet and no longer be the subject of an off-label prescription.

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Executive summary

Clinical aspects

- Menstrually related migraine (MRM) is a particular migraine subtype in which the attacks occur at the same time as or near the menstrual flow.
- Approximately 50% of migrainous women suffer from MRM.
- MRM attacks are often more severe, longer and associated with greater disability and are less drug responsive than non-menstrual attacks.

Acute treatment options

- First of all, consider abortive therapy with migraine specific drugs, primarily in triptans. Alternatively, the association of triptan plus NSAIDs (used separately or as a single tablet) could be useful in attacks that are poorly responsive to acute treatment.

Prophylactic treatment options

- If MRM attacks are refractory to the symptomatic drug, then resort to a prophylactic treatment, such as a short-term perimenstrual prophylaxis with NSAIDs, COX-2 inhibitors, long-life triptans or ergotamine derivatives. If MRM fails to respond, consider the perimenstrual supplementation with percutaneous estradiol gel, phytoestrogens or magnesium.
- In case of an 'estrogen-withdrawal headache', in which attacks appear during the hormone-free interval (HFI), it is possible to prevent the fall of estrogen levels by using a continuous regimen (i.e., continuous use of a combined contraceptive or progestogen-only contraceptive) in order to eliminate the HFI. Another option is to simply reduce the magnitude of the estrogen fall by shortening the HFI to less than the usual 7 days or by using low-dose estrogen supplementation in the HFI.
- Finally, if MRM remains refractory despite the abovementioned strategies, the drugs usually prescribed for migraine prophylaxis (e.g., propranolol, pizotifen and topiramate) can be tried, if necessary, by increasing the dosage of the drug in the perimenstrual period.

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