ORIGINAL RESEARCH ARTICLE

Clin Drug Invest 2006; 26 (5): 287-296
1173-2563/06/0005-0287/$39.95/0

Tanacetum parthenium and *Salix alba* (Mig-RL®) Combination in Migraine Prophylaxis

A Prospective, Open-Label Study

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Abstract

Background: *Tanacetum parthenium* (feverfew) has been used traditionally to treat migraine, and although its mechanism of action is not fully understood, serotonin 5-HT receptor blocking effects have been suggested. *T. parthenium* and *Salix alba* (white willow) either alone or in combination (Mig-RL®) were recently shown to inhibit binding to 5-$HT_{2A/2C}$ receptors; *T. parthenium* failed to recognise 5-HT_{1D} receptors, whereas *S. alba* or the combination did. It was hypothesised that *S. alba* in combination with *T. parthenium* may provide superior migraine prophylactic activity compared with *T. parthenium* alone.

Methods: A prospective, open-label study was performed in 12 patients diagnosed with migraine without aura. Twelve weeks' treatment with *T. parthenium* 300mg plus *S. alba* 300mg (Mig-RL®) twice daily was administered to determine the effects of therapy on migraine attack frequency (primary efficacy criterion), intensity and duration (secondary efficacy criteria), and quality of life, together with tolerability for patients.

Results: Attack frequency was reduced by 57.2% at 6 weeks ($p < 0.029$) and by 61.7% at 12 weeks ($p < 0.025$) in nine of ten patients, with 70% patients having a reduction of at least 50%. Attack intensity was reduced by 38.7% at 6 weeks ($p < 0.005$) and by 62.6% at 12 weeks ($p < 0.004$) in ten of ten patients, with 70% of patients having a reduction of at least 50%. Attack duration decreased by 67.2% at 6 weeks ($p < 0.001$) and by 76.2% at 12 weeks ($p < 0.001$) in ten of ten patients. Two patients were excluded for reasons unrelated to treatment. Self-assessed general health, physical performance, memory and anxiety also improved by the end of the study. Mig-RL® treatment was well tolerated and no adverse events occurred.

Conclusion: The remarkable efficacy of Mig-RL® in not only reducing the frequency of migraine attacks but also their pain intensity and duration in this trial warrants further investigation of this therapy in a double-blind, randomised, placebo-controlled investigation involving a larger patient population.

Introduction

Headache is one of the most common human medical complaints. During a given 12-month period most people will experience a headache.[1] The overall prevalence of migraine is 11%: 6% among men and 15–18% among women,[2] but an estimated 50% of all migraineurs are not even diagnosed.[3] Despite major recent advances in our understanding of migraine pathophysiology, migraine treatment is far from being satisfactory. Less than half the patients who are treated with a serotonin 5-$HT_{1B/1D}$ receptor agonist (triptan) drug become free of pain 2 hours later.[4] In patients with more than two migraine attacks per month, current prophylactic treatment reduces the number of attacks by up to 50%, but in only half the patients.[5] Moreover, undesirable effects encountered with prophylactic drugs are largely responsible for the high rates of treatment discontinuation.[5] There is still no effective prophylactic drug available that has specifically been developed for migraine.[2,5,6] Clearly, therefore, more effective and better tolerated prophylactic treatments for migraine are required.

Migraine is best understood as a primary disorder of the brain[2] and trigeminovascular system activation is now widely accepted as being involved in the nociceptive process by central sensitisation, sensory neuropeptide release and vasodilatation of cranial blood vessels.[2,7,8] However, the initial events that actually trigger trigeminovascular activation are not well understood.[8-11] Serotonin has been consistently implicated in migraine,[12-16] which is suggestive too of a role for its receptors. In particular, 5-HT_{1B} and 5-HT_{1D} receptors are considered to be the main molecular targets of sumatriptan and congeners in acute treatment,[17-19] whereas 5-HT_{2A} and 5-HT_{2C} receptors are targeted by 5-HT antagonists, such as methysergide, oxetorone, pizotifen and cyproheptadine, which are used in migraine prophylaxis.[5,6,14,20]

Tanacetum parthenium (feverfew) has traditionally been used as a well tolerated prophylactic treatment for migraine, but its clinical effectiveness remains to be fully established,[20,21] suggesting that *T. parthenium* alone may be insufficient to provide conclusive benefit. The mechanism of action of *T. parthenium* is not well understood, but 5-HT-receptor-blocking properties have been reported,[22-25] and inhibition of binding to 5-HT_{2A} and 5-HT_{2C} receptors, and to a lesser extent 5-HT_{1B} receptors,[26] has been suggested to play a role. In the same study, *T. parthenium* did not recognise 5-HT_{1D} receptors.[26] Interestingly, *Salix alba* (white willow), which has been traditionally used to relieve various pains including headache, was shown to strongly inhibit binding to 5-HT_{2A} and 5-HT_{2C} receptors in similar fashion to *T. parthenium*.[26] However, in marked contrast to *T. parthenium, S. alba* interacted strongly with 5-HT_{1D} receptors,[26] and combination of the two plant extracts consolidated activity at 5-HT_{2A} and 5-HT_{2C} receptors whilst maintaining activity at 5-HT_{1D} receptors.[26] The possibility is thus raised that combining *T. parthenium* with *S. alba* may provide more effective migraine prophylaxis than *T. parthenium* alone. A prospective, open-label study was therefore carried out to evaluate the efficacy of 12 weeks' treatment with standardised *T. parthenium* and *S. alba* extracts in combination (Mig-RL®; Naturveda – Vitro-Bio Research Institute, Issoire, France)[1] on attack frequency (primary efficacy criterion), pain intensity and duration (secondary efficacy criteria) in 12 patients diagnosed as having migraine without aura.

Patients and Methods

Study Design

The primary efficacy criterion was migraine attack frequency, the secondary efficacy criteria were intensity and duration of migraine attacks, and other criteria were quality of life, tolerability and adverse effects.

The study was carried out at the Department of Neurology, Centre Hospitalier Universitaire, Clermont-Ferrand, France, in accordance with the Declaration of Helsinki. Ethics committee approval was

1 The use of trade names is for product identification purposes only and does not imply endorsement.

obtained from the hospital and signed informed consent was obtained from each patient prior to inclusion in the study.

Inclusion criteria were: (a) patients diagnosed with migraine without aura according to International Headache Society (IHS) criteria,[27] as defined by The Headache Classification Subcommittee of the IHS (2004), ICH D-II code 1.1; ICD-IONA code [G43.0]; (b) males or females aged >18 years; and (c) no migraine prophylactic treatment employed for at least a month prior to the study.

Exclusion criteria were: (a) mental deficit, language barrier or incapacity to understand the study protocol or the investigators; (b) lactating or pregnant women or women able to become pregnant, i.e. premenopausal and not using adequate contraception; (c) patients with evolving neurological disorders, known previous cerebral trauma, diagnosed psychotic disorders, renal or hepatic insufficiency, or any other serious pathology; and (d) patients taking migraine prophylactic medication, corticosteroids, antidepressants or antipsychotics.

Study Protocol

Otherwise healthy men (n = 5) and women (n = 7) aged 18–55 years were enrolled after an initial consultation that comprised a medical examination and establishment of their migraine attack history. Each patient was requested to provide detailed information in a headache diary on: (a) pain perception using a visual analogue scale (VAS) rated from 0 (pain-free) to 10 (unbearable); (b) attack frequency; (c) attack duration; (d) attack intensity; (e) use of symptomatic drugs; and (f) quality-of-life-associated parameters. The patients were required to complete this diary over a 6-week baseline period and then throughout the study. Attack (pain) intensity was recorded by each patient during consultations on days 0, 42 and 84 (overall attack intensity) and 3 hours after the onset of each attack (individual attack intensity). Quality-of-life-associated parameters were self-assessed on a 0 (very poor) to 10 (excellent) VAS, and included physical and intellectual performance, dynamism, memory, capacity to relax, concentration, sociability, emotionality, irritability, anxiety, mood, sleep, interictal 'heavy head' sensation, and social and professional satisfaction. Two subsequent consultations were planned at days 42 and 84 of treatment.

Treatment

Two Mig-RL® capsules (size 1) containing standardised powdered extracts of *S. alba* 150mg and *T. parthenium* 150mg with 0.2mg copper gluconate stabiliser were administered twice daily. Hydroalcoholic freeze-dried extracts were obtained from a commercial source (Laboratoir Biosphere-99, Les Martres de Veyre, France). *S. alba* extract was standardised for salicilin (≥1.5%) and *T. parthenium* for parthenolide (≥0.2%). Both plant extracts are listed in the European Pharmacopoeia and are authorised for oral administration to human beings by the European Union Regulatory Authorities. Symptomatic medication was authorised and comprised NSAIDs, paracetamol (acetaminophen), Cafergot® (ergotamine/caffeine), metoclopramide and dihydroergotamine (DHE) spray.

Data Analysis

In view of the small group size, data were compared on days 0, 42 and 84 by one-way ANOVA followed by a *post-hoc* Student's paired t-test, provided variance was homogeneous.

Results

Patient details, migraine history, attack frequency and the symptomatic drugs used for acute pain relief during the 6-week baseline period are shown in table I. Migraine history ranged from 3 to 36 years in nine patients, with recent histories of >6 months recorded for the remaining three patients (table I). Mean patient age was 35.8 years (table I). Of the 12 patients enrolled, one (no. 10) was excluded from the study because of almost continuous headache and underwent further neurological examination for non-migrainous causes. Patient no. 11 was also excluded from the study for refusing to attend the planned consultancy, despite treatment continuation. Patient no. 2 had very frequent migraine attacks (average of 15 in the 6 weeks before

Table I. Patient details, migraine history, attack frequency and symptomatic drugs used for acute pain relief during the 6-week baseline period. Patients 10 and 11 were excluded from the study

Patient	Sex	Age (y)	Attack frequency (6-week baseline period)	Migraine history (y)	Symptomatic drugs
1	F	28	6	>0.5	Paracetamol
2	M	26	15	>0.5	DHE
3	F	27	3	14	DHE spray
4	F	55	15	22	ASA/metoclopramide
5	F	35	3	>0.5	NR
6	F	45	4.5	20	Ketoprofen
7	M	50	7.5	34	ASA/metoclopramide or ketoprofen
8	M	18	6	7	NR
9	F	49	4.5	36	DHE
10 (excluded)	F	45	18	3	Paracetamol (acetaminophen)
11 (excluded)	M	35	15	7	Ergotamine/caffeine
12	M	25	8	10	Ibuprofen
	Mean	35.8	7.3		
	SEM	12.9	4.4		

ASA = aspirin (acetylsalicylic acid); **DHE** = dihydroergotamine; **NR** = not recorded.

the study), and began treatment for another illness during the 6- to 12-week study period; data for this patient are included only up to day 42. No patients stopped taking Mig-RL® because of adverse events or intolerance.

Main Parameters

Primary Efficacy Criterion: Effects on Attack Frequency

Prior to starting Mig-RL® therapy, attack frequency ranged from 3 to 15 attacks over the baseline 6-week period (average 7.3 ± 4.4, n = 10; figure 1 and table I). After 6 weeks of Mig-RL® therapy, attack frequency diminished in eight patients, remained unchanged in one patient (no. 5 with a frequency of 3), and increased in one patient (no. 5 from 7.5 to 11). It was subsequently found that this patient had omitted to indicate that antidepressant treatment was stopped shortly before the study. The mean attack frequency at day 42 was 3.1 ± 3.0, corresponding to a 57.2% reduction ($p < 0.029$; figure 1). Over the following 6-week period, the mean attack frequency remained reduced at 2.8 ± 2.3, corresponding to a 61.7% reduction compared with day 0 ($p < 0.02$) and a further 10.4% reduction ($p = 0.80$) compared with day 42. Seventy percent of patients had a reduction in frequency of attacks of at least 50% after 12 weeks' treatment. Patient no. 7 had an attack frequency of 5 at day 84 compared with 7.5 at day 0 and 11 at day 42. Patient no. 8 had an attack frequency of 6 at day 0 and 0 at days 42 and 84. By day 84 of Mig-RL® treatment, improve-

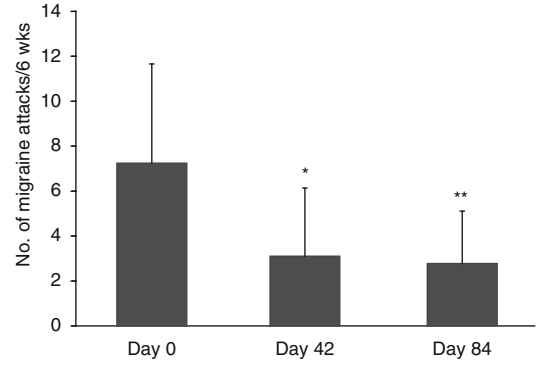

Fig. 1. Effect of treatment with *Tanacetum parthenium* plus *Salix alba* (Mig-RL®) on attack frequency (primary efficacy criterion) in ten patients with migraine without aura. Data are means (± SEM) of the number of attacks recorded by the patient over a 6-week period. p-Values are shown for comparisons with data at day 0. No statistically significant differences were noted between days 42 and 84. * $p < 0.029$, ** $p < 0.025$.

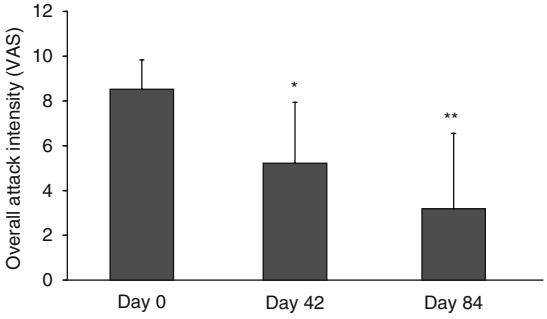

Fig. 2. Effect of *Tanacetum parthenium* plus *Salix alba* (Mig-RL®) treatment on overall attack intensity (secondary efficacy criterion) in ten patients with migraine without aura. Data are means (± SEM) of the number of the overall attack intensity on a 0–10 visual analogue scale (VAS) recorded by the patient on days 0, 42 and 84. p-Values are shown for comparisons with data at day 0. No statistically significant differences were noted between days 42 and 84. * $p < 0.005$, ** $p < 0.004$.

ments in attack frequency were seen in nine of ten patients (figure 1).

Secondary Efficacy Criteria

Effect on Pain Intensity

Mean overall pain intensity appreciation during a migraine attack was 8.5 ± 1.3 on day 0, 5.2 ± 2.7 at day 42 (corresponding to a 38.7% decrease [$p < 0.005$]) and 3.2 ± 3.4 at day 84 (corresponding to decreases of 62.6% [$p < 0.004$] compared with day 0, and 39.0% [$p < 0.22$]) compared with day 42 (figure 2). Overall attack pain intensity was decreased in all patients at days 42 and 84 (figure 2). Seventy percent of patients had a reduction of at least 50% in overall pain intensity after 12 weeks' treatment.

Mean individual attack intensity appreciation was 8.5 ± 1.3 on day 0, 5.2 ± 2.9 on day 42 (corresponding to a 39.0% decrease [$p < 0.002$]) and 4.0 ± 3.5 on day 84 (corresponding to reductions of 53.4% [$p < 0.004$]) compared with day 0, and 9.6% ($p = 0.53$) compared with day 42. Individual attack intensity was decreased in all patients at days 42 and 84. The individual attack intensity data can practically be superimposed on those of overall attack intensity (figure 2).

Effect on Attack Duration

Mean attack duration (figure 3) was 33.3 ± 14.7h at day 0, 10.9h at day 42 (corresponding to a 67.2% reduction [$p < 0.001$]) and 7.9h at day 84 (corresponding to a 76.2% decrease compared with day 0 [$p < 0.001$]) and 27.5% compared with day 42 [$p < 0.21$]). Attack duration was reduced in all patients at days 42 and 84 (figure 3).

Other Criteria

Quality of Life

Improvements in quality-of-life-associated parameters were apparent in patients' self-assessment of general health, physical performance, memory and anxiety by the end of the study (table II). Although a propensity towards improvement in these parameters was apparent on day 42, statistically significant differences were not seen until day 84 (table II).

Adverse Events and Tolerability

Mig-RL® was well tolerated in all patients and no notable adverse effects or adverse events were recorded.

Discussion

Twelve weeks of Mig-RL® therapy markedly affected the primary efficacy criterion investigated: attack frequency was reduced in nine of ten patients

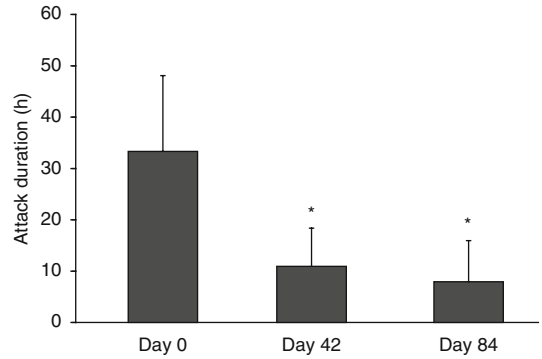

Fig. 3. Effect of *Tanacetum parthenium* plus *Salix alba* (Mig-RL®) treatment on attack duration (secondary efficacy criterion) in ten patients with migraine without aura. Data are means (± SEM) of the duration of attacks recorded by the patient over 6-week periods before (day 0) and after 6 and 12 weeks of treatment. p-Values are shown for comparisons with data at day 0. No statistically significant differences were noted between days 42 and 84. * $p < 0.001$.

Table II. Mean self-assessment scores for quality-of-life-associated parameters before (day 0), and after 6 and 12 weeks of treatment with *Tanacetum parthenium* and *Salix alba* combination (Mig-RL®)[a]

Parameter	Day 0	Day 42			Day 84		
		score ± SEM	% change	SA	score ± SEM	% change	SA
General health	5.8 ± 1.0	6.6 ± 0.9	13.8	NS	7.3 ± 1.1	25.9	$p < 0.01$
Physical fitness	5.6 ± 2.3	7.4 ± 2.1	32.1	NS	7.7 ± 2.5	37.5	NS
Intellectual performance	7.8 ± 1.7	6.9 ± 2.5	−11.5	NS	8.6 ± 1.0	10.3	NS
Dynamism	6.2 ± 2.6	6.9 ± 2.7	11.3	NS	7.9 ± 2.0	27.4	NS
Physical performance	5.5 ± 2.7	7.6 ± 1.6	38.2	NS	8.5 ± 1.3	54.5	$p < 0.02$
Body sensation	4.8 ± 2.8	4.1 ± 2.7	−14.6	NS	3.7 ± 3.3	−22.9	NS
Memory	5.8 ± 3.2	7.7 ± 1.8	32.8	NS	8.6 ± 1.4	48.3	$p < 0.05$
Capacity to concentrate	5.0 ± 3.1	6.6 ± 2.3	32.0	NS	7.6 ± 2.3	52.0	NS
Capacity to relax	4.8 ± 3.1	6.0 ± 2.9	25.0	NS	7.5 ± 3.0	56.3	NS
Sociability	6.6 ± 3.8	6.7 ± 2.8	1.5	NS	8.2 ± 2.4	24.2	NS
Emotionality	6.7 ± 2.4	6.8 ± 1.9	1.5	NS	8.3 ± 1.6	23.9	NS
Libido	7.3 ± 2.2	7.4 ± 2.0	1.4	NS	7.3 ± 2.3	0.0	NS
Irritability	5.4 ± 3.0	5.7 ± 2.7	5.6	NS	7.1 ± 2.5	31.5	NS
Anxiety	6.2 ± 2.7	5.0 ± 2.7	−16.1	NS	3.4 ± 2.6	−45.2	$p < 0.05$
Mood	5.9 ± 2.7	6.7 ± 2.8	13.6	NS	6.6 ± 2.6	11.9	NS
Sleep	5.2 ± 3.5	6.3 ± 3.4	21.2	NS	7.2 ± 3.1	38.5	NS
Interictal heavy head sensation	7.0 ± 3.0	7.3 ± 3.2	4.3	NS	5.7 ± 4.2	−18.6	NS
Social and professional satisfaction	5.8 ± 3.0	6.4 ± 3.1	10.3	NS	7.7 ± 2.8	32.8	NS
Global quality of life	5.8 ± 3.0	7.0 ± 2.6	20.7	NS	7.7 ± 2.6	32.8	NS

a Data are means ± SEM. Percentage changes are comparisons with values at day 0.

NS = not significant; **SA** = statistical analysis.

by 61.7% ($p < 0.029$), with 70% of patients experiencing a reduction of >50%. The secondary efficacy criteria of pain intensity and attack duration were reduced in ten out of ten patients by 62.6% ($p < 0.004$) and 76.2% ($p < 0.001$), respectively, with 70% of patients experiencing a reduction in intensity of >50%. In addition, Mig-RL® improved patient self-assessment of general health, physical performance, memory and anxiety by the end of the 12-week treatment period, and was well tolerated with no adverse effects. Importantly, attack frequency, pain intensity and duration were all reduced significantly by 6 weeks, and a further slight but non-significant reduction was noted after 12 weeks. These data suggest that Mig-RL® can produce effective migraine prevention by 6 weeks. In addition, Mig-RL® also notably produced a 'psychological' improvement, as shown by self-assessed general, physical and mental health, which became significant by the end of the study. Indeed, seven out of ten patients expressed their wish to continue the treatment.

In double-blind, randomised, placebo-controlled investigations of *T. parthenium* prophylaxis in migraine (summarised in table III), attack frequency was significantly reduced by 23.4%,[28] 39.2%[29] and 45.2%,[30] with no changes reported by De Weerdt et al.[31] and Pfaffenrath et al.[32] A placebo response of approximately 30% is generally observed in migraine prophylaxis studies.[6,33] Interestingly, in the study by Murphy et al.,[28] when data were divided into patients with migraine and aura and those with migraine but no aura, attack frequency was significantly reduced by 32.6% in patients with aura compared with a non-significant 20.4% reduction in patients without aura. These observations suggest that *T. parthenium* is less effective in preventing migraine without aura than that with aura. In all the reported placebo-controlled trials of *T. parthenium* (table III), no distinction was made between patients presenting migraine with or without aura, with the exception of that by Murphy et al.[28] Although further investigation will be required to confirm this observation, it may nevertheless suggest that Mig-RL® could be even more efficacious in reducing attack frequency in patients presenting migraine with aura, although there are no data to support this at present.

It has recently been observed that *S. alba,* like *T. parthenium,* recognises 5-HT_{2A} and 5-HT_{2C} receptors, and, unlike *T. parthenium,* also recognises 5-HT_{1D} receptors.[26] Although the mechanism of action of *T. parthenium* in migraine prevention is still a matter of debate, two possible hypotheses arise from this observation. Firstly, if indeed 5-HT_{2A} and/or 5-HT_{2C} receptors play a role in migraine prophylaxis,[5,6,14,20] *S. alba* may consolidate the effects of *T. parthenium* on attack frequency. Secondly, since *S. alba*, but not *T. parthenium*, interacts with 5-HT_{1D} receptors in a positive cooperative manner,[26] *S. alba* may favour the effects of endogenous serotonin at these receptors during trigeminovascular activation, resulting in a triptan-like effect (i.e. reducing neuronal firing, reducing the release of sensory neuropeptides, ensuing cranial vasodilatation and neurogenic inflammation). Consequently, pain intensity and duration may be expected to be reduced by *S. alba* by this mechanism over and above any beneficial (non-5-HT_{1D} receptor) effect mediated by *T. parthenium*. The well known anti-inflammatory activity of *S. alba*[35] is weak and ostensibly seems unlikely to play a major role in the migraine-preventive effects of Mig-RL®. Interestingly, however, parthenolide, purported to be the main active ingredient of *T. parthenium*, has been reported to act on the transcription factor nuclear factor (NF)-κB,[36,37] which activates inflammatory gene expression,[37] and on IκB kinase β (IKKβ), which regulates NFκB activity.[38] Such activity is compatible with neurogenic antiphlogistic activity in the trigeminovascular system[39] and could even underlie central sensitisation,[37,39] currently considered to be involved in migraine-associated allodynia.[40] These properties of *T. parthenium* could therefore provide additional anti-inflammatory properties to those of *S. alba* alone, and thus contribute to the migraine prophylactic efficacy of Mig-RL®. In the current study, the combination of *T. parthenium* and *S. alba* was remarkably effective in reducing attack frequency, pain intensity and duration, findings that are supportive of synergistic

Table III. Summary of published double-blind, randomised, placebo-controlled clinical trials of *Tanacetum parthenium* prophylaxis in migraine

Reference	Design	No. of patients	Migraine type	*T. parthenium* dose (mg)	Total dose (mg/day)	Treatment duration (wks)	Overall result	Key findings
Johnson et al.[30]	Parallel (withdrawal)	17	With and without aura	25 bid	50	24	+	45.2% reduction in attack frequency ($p < 0.02$)
Murphy et al.[28]	Crossover	72	With and without aura	82/day	82	16	+	Overall: 23.4% reduction in attack frequency ($p < 0.005$) With aura: 32.6% reduction in attack frequency in 17 patients ($p < 0.05$) Without aura: 20.4% reduction in attack frequency in 42 patients ($p = 0.06$)
De Weerdt et al.[31]	Crossover	50	With and without aura	143/day	143	8	−	No change in attack frequency or pain intensity
Palevitch et al.[34]	Open preliminary phase followed by double-blind parallel (withdrawal)	57	With and without aura	50 bid	100	8	+	Reduction in pain intensity ($p < 0.01$)
Pfaffenrath et al.[32]	Parallel (dose-finding)	147	With and without aura	2.08 tid	6.25	12	−	No effect on attack frequency only
				6.25 tid	18.75	12	−	No effect on attack frequency only[a]
				18.75 tid	56.25	12	−	No effect on attack frequency only
Diener[33]	Parallel	170	With and without aura	6.25 tid	18.75	16	+	39.2% reduction in attack frequency ($p < 0.05$)

a Although 21.6% reduction in attack frequency ($p < 0.02$) in a patient subgroup with at least four attacks per month.

bid = twice daily; **tid** = three times daily; **+** = positive; **−** = negative.

activity. Indeed, a marked reduction in attack frequency occurred in all but one of the patients. This is a notable preliminary result given that conventional prophylactic treatments reduce attack frequency in only around half of patients.[5]

The total daily doses of *T. parthenium* and *S. alba* employed were 600mg each, which is higher than those reported in previous studies. Although the number of patients investigated was small, no notable adverse effects or adverse events were noted and Mig-RL® was well tolerated. However, since two capsules were to be taken twice a day, three out of ten patients complained about the number of capsules that had to be taken, and the fact that they had to be taken more than once a day.

The main limitations of the study are inherent in its design, namely the absence of placebo control and the small number of patients investigated, which underpowers the trial. It is probable that there was a considerable placebo effect in this trial,[33,41] and comparisons with randomised, placebo-controlled trial data are therefore difficult. The results of open-label trials in migraine prophylaxis should be treated with caution.

Conclusion

Notwithstanding the study's limitations, the objectives of this open-label, investigational trial were largely attained. The remarkable results obtained with Mig-RL® with respect to attack frequency, pain intensity and attack duration justify a randomised, placebo-controlled study in a larger population of migraineurs, including those with aura. Importantly, the over-the-counter availability of Mig-RL® may help improve the lives of the large numbers of headache sufferers, including the 50% of all migraineurs who have never been diagnosed or who are reluctant to consult their doctor.[3]

Acknowledgements

The study was sponsored by the Naturveda – Vitro-Bio Research Institute. Dr J.C. Pechadre received an honorarium for this work from The Vitro-Bio Research Institute. This paper is dedicated to Dr Pechadre's memory.

The other authors have no potential conflicts of interest that are directly relevant to the contents of this study.

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