Real world, open label prospective experience of supplementation with a fixed combination of magnesium, vitamin B2, feverfew, andrographis paniculata and coenzyme Q10 (Vivinor®) for episodic migraine prophylaxis

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Abstract

Background

To investigate efficacy and safety of a supplementation with a fixed combination of magnesium, vitamin B2, feverfew, andrographis paniculata and coenzyme Q10 (Vivinor®) in episodic migraine prevention.

Methods

An observational, prospective, real-world study was conducted. After a one-month baseline period, Vivinor® was introduced in 113 Greek patients with episodic migraine who were prospectively followed-up for three months. The primary endpoint was the change in monthly migraine days between baseline period (BL) and the third month of supplementation (T3). Secondary endpoints included changes in mean intensity of migraine and in days with use of acute migraine medications. Changes in scores of Migraine Disability Assessment questionnaire (MIDAS), Headache Impact Test-6 (HIT-6), Migraine Therapy Assessment questionnaire (MTAQ), MSQ-QOL (Migraine-Specific Quality of life questionnaire), HADS (Hospital Anxiety and Depression Scale) were also evaluated. Those with ≥ 50% reduction in monthly migraine days at T3, compared to BL were considered Vivinor®-responders.

Results

Mean number of migraine days was significantly decreased between BL and T3 (9.9 ± 5.0 vs 6.2 ± 4.0; $P < 0.001$). Likewise, days with peak headache intensity of > 4/10 (8.3 ± 3.8 vs 5.8 ± 4.0; $P < 0.001$) as well as days using acute headache medications per month (9.8 ± 5.6 vs 7.2 ± 5.4; $P < 0.001$) were significantly reduced. At final visit, 64 patients (56.6%) were classified as responders. The beneficial effect of Vivinor® supplementation was also associated with significant changes in HIT-6, MIDAS, MTAQ and MSQ-QOL scores between BL and T3. There were no safety concerns.

Conclusions

Vivinor® appears to be an effective and well-tolerated preventive treatment against episodic migraine.

Trial registration

NCT04463875, Registered 9 July 2020- Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT04463875

Background

Migraine, a common primary headache disorder, ranks among the leading causes of all disease-associated disability worldwide and constitutes the major cause of disability among neurological disorders.[1] Based on its frequency, migraine can be classified as episodic (less than 15 days monthly) or

chronic (more than 15 headache days monthly, of which at least 8 are of migrainous type or respond to migraine-specific medication, for more than 3 months) [2]

Apart from the use of the number of monthly migraine days to classify migraine in its episodic (EM) or chronic (CM) form, there are other phenotypic differences that can facilitate distinguishing the two conditions in order to establish a proper diagnosis. Generally, patients with EM have shorter average duration of headache, while they also experience less pain intensity, milder pain-associated autonomic symptoms, as well as pain-related comorbidities, compared to their counterparts with CM.[3]

The course of both EM and CM over time, as well as the relationship between these conditions are vaguely defined. There is evidence from large population-based studies that patients with EM can remit, remain stable, or even progress to CM at a rate of 2.5% per year, whereas the inverse can also occur, with an estimated 26% transition rate of CM to EM over a period of two years.[4,5]

As such, apart from reducing migraine frequency, an additional critical goal of migraine prevention treatment is to hamper progression of EM to CM. So far there are no consensus guidelines clearly defining a specific phenotype in EM patients, which would likely benefit from prophylactic first-line therapies. Nonetheless, according to widely acknowledged guidelines, migraine prophylaxis should be considered when the frequency, intensity and duration of migraine attacks impose significant disability despite appropriate use of acute medications; when the frequency of migraine attacks and the excess use of acute medications make patients more liable to medication overuse headache (MOH); but also in patients with medical contraindications to acute migraine therapies. As already mentioned, an ultimate goal may be preventing progression of EM to CM.[6]

Many conventional pharmacological medications are currently used in episodic migraine prophylaxis, including antihypertensives, antiepileptic drugs, beta and calcium channel blockers, and also various antidepressants. However, despite the fact that earlier studies indicate that treatment options with higher efficacy rates are preferred by patients even if side effects are present,[7] more recent data clearly show that the use of the pharmacological preventive approaches is commonly associated with modest response, poor adherence and compliance[8] and a significant percentage of treatment discontinuations, estimated to be as high as 55% after 12 months of treatment.[9] Since adverse events are the most common reason for early discontinuation of a migraine preventive treatment,[9] it may be concluded that although efficacy may by high in patients' preferences when starting a treatment, safety and tolerance probably play the most crucial role on the decision of stopping it early. In a more recent study from Greece, an astonishing 63% of participants claimed they would prefer the use of a neurostimulator for preventive treatment of migraine, over just 37% that preferred a pharmacological option,[10] possibly reflecting the need for treatments that better balance efficacy and safety than traditional pharmacological treatments. Unfortunately, this study did not include the option of a nutraceutical treatment in the questionnaire used.

Generally, various nutraceuticals and nutritional supplements are widely utilized for migraine prophylaxis and may be a preferred option for patients with contraindications for pharmacological treatments, failure of previous treatments due to safety or tolerability or patients' reluctance to use pharmacological treatments due to such concerns. A supplementation with a fixed combination of five nutraceutical agents, i.e., magnesium 281.25 mg, vitamin B24.8 mg, feverfew150mg, coenzyme Q10 20 mg, and andropraphis paniculata 100 mg (Vivinor®; Brain Therapeutics, Greece) is available in Greece and other European Union countries for migraine prevention. In our study, Vivinor® was investigated for its preventive ability in a population of Greek patients with episodic migraine. We hereby report the outcome of this intervention.

Methods

Study design

This open-label, single-arm, prospective, multicentre, observational study was conducted in five headache outpatient centres located in five different nodal geographic locations of Greece, including the major urban areas of Athens, Thessaloniki, Patras, Kalamata and the island of Corfu. In accordance with the principles of the Helsinki Declaration as also with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines, eligibility was confirmed by a protocol-specific checklist and written informed consent was obtained from each patient. The study was approved by the principal investigator's Institutional Review Board (Mediterraneo Hospital, Athens, protocol no 2718, 26 March 2018) and is registered at clinicaltrials.gov (NCT04463875)

Patient selection

Participants were adult patients with a documented history of episodic migraine with or without aura for more than the 12 months prior to screening, according to the criteria of the International Classification of Headaches Disorders-III (IHS, 2013).[11] The following inclusion criteria were applied: (1) established diagnosis of episodic migraine with or without aura for more than one year prior to study entry; (2); evidence of 4-14 migraine days per month during the last trimester prior to screening; (3) participants may had been either treatment-naive or not suitable for or had failed previous migraine pharmacological prophylactic treatments (4) were able to fully understand protocol and study information provided by the investigators and (5) enrolled patients should take no other preventive treatment or use any other migraine prophylactic method during the three months before entering the study and throughout the study period.

We excluded patients having the following criteria: (1) older than 50 years of age at migraine onset; (2) evidence of MOH; (3) pregnant or nursing females; (4) history of tension-type, cluster or hemiplegic headache; (5) history of severe anaphylactic reactions to any of the intervention's ingredients; (6) evidence of severe systemic diseases and (7) history or evidence of major psychiatric disorder.

Supplementation

After a one-month headache diary completion baseline phase, patients were started on three-month supplementation with one or two tablets Vivinor® daily, comprising of 281,25 mg Magnesium, 4.8mg vitamin B2, 20mg coenzyme Q10, 150mg feverfew and 100mg andrographis paniculata, according to their treating physician's decision and to standard clinical practice. The supplementation was given at a stable dose from onset through the end of study without up-titration. No deviation from the maximum target dose of two tablets per day was allowed. Demographic and clinical baseline data as well as response and safety profile of Vivinor® supplementation were recorded and analyzed.

Assessments

At baseline visit (V1) and after the informed consent procedure had been completed, physicians collected each patient's demographic data, as well as migraine clinical phenotype characteristics, medical and migraine history, information on migraine attacks, associated symptoms and acute attack medications. A paper case report form (CRF) was used. V1 was followed by a one-month observation period (baseline phase, BL). During baseline patients were asked to complete a paper headache diary on a daily basis that included characteristics of the migraine phenotype, including number of days with migraine per month, headache intensity, associated symptoms, and use of acute medications.

At second visit (V2; Day 30 ± 10 since V1), patients experiencing between 4-14 migraine days during baseline period were started supplementation with Vivinor®. From V1 onwards until the end of the study at V3 (Day 120 ± 10), all patients kept the same paper headache diary in which they reported changes in the above-mentioned migraine characteristics longitudinally over time.

Efficacy evaluation

The primary objective of our study was to evaluate the efficacy of Vivinor® supplementation, as expressed by the change in mean number of migraine days between baseline period and the third month of supplementation (T3). Secondary objectives included change in migraine severity between baseline and third month of supplementation as expressed by the change in the number of days with peak migraine intensity of more than 4 out of 10 in a 0-10 numerical scale (moderate/severe pain), and the change in days with any acute migraine medications used. Changes in scores of the Headache Impact Test- 6 (HIT 6);[12] Migraine Therapy Assessment questionnaire (MTAQ);[13] MSQ (Migraine-Specific Quality of life) questionnaire[14] and of the Hospital Anxiety and Depression Scale (HADS)[15] were assessed between BL vs T3 as additional secondary endpoints. Change in *Migraine* Disability Assessment questionnaire (MIDAS)[16] scores between V2 and V3 was also a secondary endpoint.

Finally, data on patients' preference and decision to continue treatment were also collected and analyzed. Patients with ≥50% (clinically significant) reduction in median migraine days during T3 compared to BL were considered responders. Responders were further sub-classified as moderate responders (at least 50% reduction in migraine days); very good responders (at least 75% reduction in migraine days) and excellent responders (100% reduction in migraine days – migraine free).

Safety evaluation

Current literature shows that supplementation with these specific active ingredients is safe and generally well tolerated[17] and as such no clinically-significant adverse events related to its use were expected to occur. Nonetheless, patients were encouraged to report any adverse events occurring throughout the study period either spontaneously or in response to general, indirect questioning. Each investigator was responsible for documenting the type and severity of overall adverse events and then categorized them for potential relationship to the supplementation given. Patients who received at least one dose of supplementation underwent safety evaluation.

Statistical analysis

This was an exploratory study and as such no adjustment by multiplicity was made to account for the various endpoints considered. Sample size was determined in order to detect with a power of 80% and one-side 10% level of significance a 50% reduction in mean migraine days at the end of the study. To account for premature withdrawal of patients from the study, we increased the sample size by 5%.

Results were analysed on an intention-to-treat basis. The primary intent-to-treat analysis included all enrolled patients (ITT population). A secondary efficacy analysis was performed on those patients who completed the trial (EFF population), ie., daily supplementation with a stable Vivinor® dose for 3 months. The primary efficacy variable (change in mean migraine days) was analysed for both ITT and EFF populations. For the ITT analysis, early withdrawers for any reason, including perceived lack of efficacy, adverse events, intolerance or other were counted as non-responders per se.

Descriptive data analysis included categorical variables presented in counts and weighted percentages, and continuous variables as mean or median with the corresponding standard error or range, depending on the nature of the variable. The changes in median clinical scores from BL vs T3 were assessed using paired samples t-tests, after checking whether the variables followed the normal distribution with the Kolmogorov-Smirnov test. The X^2 test was used to ascertain differences between categorical variables. All tests were two-sided, unless otherwise stated, and calculations were performed using SPSS software package version 23.0 (SPSS Inc., Chicago, Ill). P values of <0.05 were considered significant.

Results

A total of 113 patients were enrolled and all of them successfully completed the study. Among them, 54 (47.8%) were preventive treatment-naïve for their migraine, whereas 59 (52.2%) patients had failed in a mean number of 2.3 ± 1.1 (range: 1-5) previous medications, like flunarizine, valproic acid, topiramate, propranolol and amitriptyline. Hence, both the ITT and EFF populations were comprised of the same sample size of 113 patients. Their demographic and baseline clinical characteristics are summarized in table 1.

The analysis of the primary response variable (n=113) showed that there was a statistically significant decrease in mean migraine days between BL and T3 (9.9 ± 5.0 vs 6.2 ± 4.0; P < 0.001). Moreover, migraine severity was also significantly decreased as measured by the change in the number of monthly days with peak migraine intensity of more that 4 (moderate/severe pain) in a 0-10 numerical scale between BL and T3 (8.3 ± 3.8 vs 5.8 ± 4.0; P < 0.001). Supplementation with Vivinor® was also associated with a significant reduction in days using acute migraine medications per month between BL and T3 (9.8 ± 5.6 vs 7.2 ± 5.4; P < 0.001).

At V3, 64 patients (56.6%) had experienced a ≥50% reduction in mean migraine days during the third month of supplementation compared to baseline period and were therefore classified as responders. Among all (n=64) responders, 59 achieved response at 50% (52.2%) and 5 at 75% (4.4%). The remaining 49 patients (43.4%) reported less than 50% reduction with Vivinor® supplementation. It should be noted that 7 of them (6.2% of non-responders) achieved a moderate 30-49% reduction in migraine days. Among the remaining non-responders, 22/42 (19.5%) experienced no benefit at all, while 20/42 (17.7%) patients achieved less than a 30% reduction in mean migraine days.

The rate of responders at ≥50% to supplementation as well as its beneficial effect in changes in mean migraine days, migraine severity, and days using acute headache medications between V2 and V3 remained unrelated to age, gender or any other baseline demographic or other neurological characteristic of patients, including supplementation dosage with either one (n=26; 23%) or two Vivinor® tablets (n=87; 77%) per day at maintanance (Spearman's rho; p=0.570).

As can be seen in table 2, the beneficial effect of Vivinor® supplementation was also associated with statistically significant changes in secondary endpoints, i.e. HIT 6, MTAQ and MSQ-QOL scores between BL and T3 and in MIDAS scores, between V1 and V3. In contrast, HADS scores remained unchanged over time. The clinically significant improvement in migraine frequency and severity at V3 compared to V2 was strongly associated with better QOL outcomes (p<0.001) according to MSQ-QOL questionnaire scores. Notably, a total of 70 participants declared that they were satisfied from the study intervention and wished to continue further supplementation after the completion of the study.

Vivinor® supplementation also proved to be safe and well tolerated. In total, 5 patients reported diarrhea, which was mild in all cases and patients were able to complete study with some temporary adjustment in their diet. No other adverse events were reported.

Discussion

The pathophysiology of migraine involves dysfunction of subcortical structures modulating sensory input in the trigeminovascular system. As a result, vasoactive peptides, such as *calcitonin gene-related peptide* (*CGRP*) and substance P, are released from trigeminovascular neurons, thereby exacerbating vasodilation and generating neurogenic inflammation.[18,19] Mitochondrial dysfunction, increased calcitonin, matrix metalloproteinase 9 (MMP-9), and nitric oxide (NO) levels, as well as decreased level of

metabolic enzymes are also considered among the significant factors generating migraine.[20] Additionally, genetic and environmental factors might also be involved in triggering the

onset of migraine attacks.[21]

Various conventional pharmacological treatments for migraine prevention are currently in use, aiming to reduce afferent traffic or stabilizing these above-mentioned abnormal pathways.[18] Nonetheless, many patients respond poorly to, or experience adverse events with these treatments.[8] In addition, many patients are noncompliant with these medications; unsatisfactory efficacy, safety or tolerability issues, and concerns about long-term safety are among the reasons.[9]

As such, there is a growing therapeutic shift over the last years towards treatments with lower adverse event rate, including onabotulinum toxin–A, monoclonal antibodies, external neurostimulators[22-24] and nutraceuticals. Nutraceuticals is a non-pharmacological approach that includes vitamins, minerals, and herbs in the prevention of migraines. The level of evidence to support use of nutrients is low or moderate, mainly because of lack of rigorous clinical trials. Nonetheless, patients often prefer nutraceutical treatment over traditional pharmacological approaches in migraine prophylaxis to diminish possible side effects and intolerance, but also based on the belief that herbal remedies or nutrients are much safer than drugs.[25,26]

The use of nutraceuticals is included or accepted by various guidelines despite the rather poor or moderate level of evidence, in both the EU and US,[6,17] based on the luck of significant adverse events and the potential of an individual or synergistic ability to target significant factors involved in migraine pathogenesis.[25] Interestingly, the Canadian Headache Society Guideline for Migraine Prophylaxis[27] includes riboflavin, coenzyme Q10, and magnesium citrate to the list of prophylactic drugs that received a strong recommendation for use, along with topiramate, propranolol and amitriptyline, among others. This recommendation comes despite the rather poor or moderate level of evidence, as authors of the Canadian Headache Society Guideline for Migraine Prophylaxis acknowledge, and is mainly based on the safety and tolerability profile, an approach which seems rational and reflecting the real-world situation.

Indeed, existing knowledge shows that magnesium, vitamin B2, feverfew and coenzyme Q10 are helpful in migraine prophylaxis with minimal safety issues, as these nutrients might be able to target some of the processes involved in migraine pathogenesis.[28] Specifically, magnesium blocks glutamate receptors, modulates ATP production and glucose metabolism and as such high dose supplementation is able to decrease glutamate-activated cortical spreading depression. Likewise, high dose supplementation with vitamin B2 and coenzyme Q10 may augment activity of mitochondrial complexes to prevent mitochondrial dysfunction. Finally, the use of feverfew is attributed to its properties to inhibit serotonin release from platelets and evoke vascular smooth muscle relaxation (Tepper et al, 2006; Nattagh-Eshtivani et al, 2018).[25,29]

In the current setting, we documented a significant improvement in all primary and secondary efficacy variables after 3 months of supplementation with a proprietary fixed combination of magnesium, vitamin B2, feverfew, coenzyme Q10 and androgrpahis paniculata. A total of 64/113 (56.6%) enrolled patients obtained a response rate at ≥50%, which was associated with improved HIT-6, MIDAS, and MSQ-QOL scores ($p<0.001$). An even larger group of patients (n=70; 62%) remained satisfied from Vivinor® and wished to continue supplementation, thoroughly bolstering the view that some *migraineurs* prefer nutraceutical over pharmacological approaches in order to avoid side effects even if the response is less clinically significant, i.e. at 30%. Notably, more than half of our patients had tried up to five previous prophylactic pharmacological medications before being supplemented with Vivinor® and either experienced modest efficacy or poor tolerance due to side effects. As such, based on their experience, they

preferred to use a potentially less effective but completely safe complementary medication as monotherapy. Patient satisfaction and a decision to continue a specific preventive migraine treatment is important in clinical practice and may not always be completely related to outcomes usually used in clinical trials. In other words, patients experiencing modest improve, less than the 50%, may be satisfied and willing to continue or repeat a treatment if they experience little or no side effects and are confident that severe side effects are unlikely in the future. On the other hand, a patient experiencing significant improvement may be reluctant to continue or repeat a treatment because of concerns with current or potential side effects or long-term safety.

Finally, another main observation of the current study is that none of the enrolled patients discontinued supplementation early throughout the process due to intolerable adverse events. Our results, overall, are in agreement with a previously published study applying a similar study design to test a proprietary supplement containing feverfew, magnesium and Q10.[30] Improvement of migraine symptoms with a proprietary supplement containing riboflavin, magnesium and Q10 was also noted in a randomized, placebo-controlled, double-blind, multicenter trial enrolling 130 migraineurs, although reduction of migraine frequency showed only a trend towards statistical significance between active and placebo arms.[31] Different dosages and formulations as well methodological issues in the study design (observational open-label vs placebo-controlled study design) may account for the discrepancy between results of the latter trials.

To conclude, our real-world experience with Vivinor® showed that this supplementation may be an effective and well tolerated complementary treatment in EM prophylaxis. However, the pilot open-label design of this trial, the lack of a control group. and the potential for selection or response bias, also present in other similar studies, can be acknowledged as significant limitations. Nevertheless, and to best possibly support the positive outcomes of Vivinor® supplementation, we used migraine-specific tools as endpoints to assess changes in disability, psychological burden, QOL, and satisfaction in close relation to the intervention we tested. Further larger placebo-controlled trials are warranted to confirm our results on the potential beneficial effect of this proprietary supplement (Vivinor®; Brain Therapeutics, Greece),

containing magnesium, vitamin B2, feverfew, coenzyme Q10 and andrographis paniculata in EM prophylaxis.

Coclusion

Vivinor® appears to be an effective and well-tolerated preventive treatment against episodic migraine.

Declarations

- Ethics approval and consent to participate

The study was approved by the principal investigator's Institutional Review Board (Mediterraneo Hospital, Athens, protocol no 2718, 26 March 2018)

- Consent for publication

All participants have given signed consent for publication ofi the present material.

- Availability of data and materials

All data and materials are available to request.

- Competing interests

No author or any immediate family member has financial relationships with commercial organizations that might appear to present a potential conflict of interest with the material presented.

- Funding

No funding source had a role in the preparation and conduction of this trial or in the preparation of the manuscript and the decision to submit it for publication. Article-processing charges were covered by Brain Therapeutics.

- Authors' contributions

MV, KS, EK, AA and ED designed the protocol. MV, AA, KS, PS and ED recruited patients and performed the assessments. AA performed the statistical analysis. AA, MV, PS and KS drafted the manuscript. MV, GV, EK and AA reviewed critically the final draft. All authors read and approved the final manuscript.

- Acknowledgements

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Tables

Table 1. Patients' baseline and clinical characteristics.

Variable	*Study samplen=113*	N	%
Sex MalesFemales	20	17.793	82.3
Age ± SDHeight in cm ± SDWeight in kgr ± SD	39.1 ± 12.4168.4 ± 7.864.5 ± 10.7		
Age at migraine onset	44	38.9	
10-18 years	14.2	8	
18-25 years	24	21.2	
25-30 years			
30-40 years			
40-50 years			
Migraine type			
Aura	43	38.1	
Non-Aura	7.1	2	1.8
	89	78.8	
Vivinor® (tb) dose 1 tablet / day2 tablets / day	26	23.0	87 77.0

Table 2. Changes in outcome measures assessing secondary efficacy variables from baseline (BL) to the last month of trimester (T3) of supplementation with Vivinor® in 113 patients comprising both the efficacy and intention to treat population (for MIDAS, changes between V1 and V3 are reported)

Tools assessing secondary endpoints	BL Mean ± SD Median	T3 Mean ±SD Median	P value
HIT-6	68.6 ± 5.7 69	63.8 ± 10.3 63	P < 0.001
MIDAS	67.0 ± 43.8 58	49.5 ± 41.0 30	P < 0.001
MTAQ	2.9 ± 1.1 3	3.2 ± 0.9 4	P < 0.001
MSQ-QOL total	52.3 ± 15.4 52	71.3 ± 10.4 71	P < 0.001
HADS-A	8.3 ± 5.8 6	8.3 ± 8.5 7	P = 0.923
HADS-D	5.7 ± 3.7 5	6.1 ± 5.2 4	P = 0.216

Abbreviations: Headache Impact Test- 6 (HIT 6); *Migraine* Disability Assessment questionnaire (MIDAS); Migraine Therapy Assessment questionnaire (MTAQ); Migraine-Specific Quality of life questionnaire (MSQ-QOL) and Hospital Anxiety and Depression Scale (HADS) anxiety (a) and depression (d).