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Simvastatin and Vitamin D for Migraine Prevention: A Randomized Controlled Trial

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Abstract

Objective—To assess efficacy and tolerability of simvastatin plus vitamin D for migraine prevention in adults with episodic migraine.

Methods—We performed a randomized, double-blind, placebo-controlled trial with a 12-week baseline period and 24-week intervention period in 57 adults with episodic migraine. Participants were randomly assigned to simvastatin 20 mg tablets twice daily plus vitamin D3 1000 international units capsules twice daily or matching placebo tablets and capsules.

Results—Compared to placebo, participants using simvastatin plus vitamin D3 demonstrated a greater decrease in number of migraine days from the baseline period to intervention weeks 1-12: a change of -8.0 (IQR: -15.0 to -2.0) days in the active treatment group versus +1.0 (IQR: 1.0 to +6.0) days in the placebo group, P<0.001; and to intervention weeks 13-24: a change of -9.0 (IQR: -13 to -5) days in the active group versus +3.0 (IQR: -1.0 to +5.0) days in the placebo group, P<0.001. In the active treatment group, 8 patients (25%) experienced 50% reduction in the number of migraine days at 12 weeks and 9 (29%) at 24 weeks post randomization. In comparison, only 1

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patient (3%) in the placebo group (p=0.03) experienced such reduction. Adverse events were similar in both active treatment and placebo groups.

Interpretation—The results demonstrate that simvastatin plus vitamin D is effective for prevention of headache in adults with episodic migraine. Given statins ability to repair endothelial dysfunction, this economical approach may also reduce the increased risk for vascular diseases among migraineurs.

Introduction

Migraine is a primary headache disorder affecting 18% of women and 6% of men in the U.S. yearly and ranks as the eighth highest cause of disability worldwide.[1, 2] Migraine typically presents during adolescence with infrequent attacks that usually respond well to common analgesics and sleep.[3, 4] Over time, attacks tend to increase in frequency and severity, leading many patients to require both abortive medication to terminate attacks and daily migraine prophylactic medication to prevent attacks.[5, 6] Additional goals of prophylaxis are to improve quality of life by decreasing physical, mental, and financial burden; and reduce the risk of progression to chronic daily headache, which is associated with high frequency migraine.[6-9] Anticonvulsants, beta-blockers, and tricyclic antidepressants are the most commonly used prophylactic medications.[10, 11]However, despite proven efficacy for migraine, their use is limited by intolerable side effects, including undesirable weight gain or loss, hypotension, cognitive slowing, somnolence, and/or fatigue.[10-12] Therefore, it is essential to identify more tolerable, efficacious options.

Migraine is primarily considered to be a neurological disorder; however, it is also associated with increased risk for vascular disease, including stroke, myocardial infarction, retinal vasculopathy, peripheral artery disease, and cardiovascular mortality.[13-19] Many of these conditions are preceded by alterations in vascular tone, reactivity, blood fluidity, and inflammation, all of which are mediated by the endothelium.[20-24]

Statins, best known for lowering cholesterol, also have cholesterol-independent effects, and have been shown to improve endothelial dysfunction,[25-30] reduce vascular wall inflammation,[27, 29, 31-35] and decrease platelet aggregation,[28, 29] and may improve autonomic function and sympathetic reflex regulation.[36] We previously observed a potential benefit and favorable interaction between statin and higher vitamin D levels on migraine.[37] Assuring protection against vitamin D deficiency when using a statin, in theory, may synergistically augment anti-inflammation and improve endothelial dysfunction,[38-40] and provide protection against statin-associated musculoskeletal pain,[41-43] estimated to occur in about 5% of those using statins.[44]

The objective of this study was to evaluate the efficacy of combination therapy with statin and vitamin D for migraine prevention, using a randomized, double-blind, placebo-controlled, parallel-arm study design.

Subjects and Methods

All study visits took place at Beth Israel Deaconess Medical Center (BIDMC), Boston, MA (September 2010-March 2013). Participants were recruited from the greater Boston area using advertisements and flyers placed in public areas and in headache, neurology, and primary care practices, and through physician referral. The BIDMC Committee on Clinical Investigations approved the study and all participants provided written informed consent. The study was registered with ClinicalTrials.gov (NCT01225263).

Screening and Eligibility Criteria

Individuals with episodic migraine were eligible if they were ≥18 years old, had migraine for ≥3 years, and had migraine ≥4 days/month. Migraine diagnosis was based on International Headache Society for headache classification (ICHD-II) criteria.[45] Individuals were ineligible if they had chronic pain conditions on a daily/near daily basis, including chronic daily headache, (defined as ≥15 headache days/month for ≥3 months); chronic opioid use; conditions requiring statin therapy, e.g., severe hypercholesterolemia, coronary heart disease, peripheral vascular disease, or diabetes; contraindications to simvastatin; severe renal disease (i.e., glomerular filtration rate <30 ml/min); creatine kinase >3 times the upper limit of normal, aspartate aminotransferase or alanine aminotransferase >2 times the upper limit of normal; or hypercalcemia. Individuals who were pregnant, nursing, or potentially could become pregnant and were unwilling to use contraception during the study were also ineligible.

Study Procedures

This 36-week study consisted of a 12-week pre-randomization baseline period (designated “weeks -12 to 0”), followed by 24-weeks of intervention (“weeks 1-12” and “weeks 13-24”). Following telephone screening, participants attended four research visits: a screening visit and three subsequent visits, at 12-week intervals. Participants continued use of their abortive and prophylactic migraine medications, but were asked to keep their migraine treatment regimen stable, to the extent possible, for the study's duration. Those with ≥4 migraine days/month who did not meet criteria for chronic daily headache (≥15 days/month for 3 months) were randomized after 12 weeks. Randomization was performed by a co-investigator (MAM), with no participant contact, using a computer generated random permuted block scheme using a macro to create 1:1 allocation with random block sizes of 2 and 4. The randomization schedule was securely delivered from MAM to the BIDMC Research Pharmacy, which assigned and dispensed the study agents to the Clinical Research Center in containers labeled with participant's name and medical record number, but which otherwise had identical labeling. A blinded Clinical Research Center nurse then provided the study agents to participants following their enrollment in the study by the study physician, Dr. Buettner. This method ensured participants, investigators and study personnel having participant contact and/or assessing outcomes at visits or entering data following visits remained blinded to treatment assignments following randomization.

Throughout the entire study, participants completed paper headache diaries tracking migraine days, duration, severity, associated symptoms, and type and dose of medications

used. In addition, every 12 weeks, participants completed three-day paper physical activity and diet diaries throughout the study. At each visit, participants were interviewed, had blood drawn, completed standardized questionnaires on migraine disability (migraine disability assessment questionnaire [MIDAS]) and non-headache body pain (Brief Pain Inventory Short-Form [BPI]), and were counseled on maintaining appropriate calcium intake. Participants were asked about potential adverse effects at each visit. Following randomization, participants also reported any missed study medication doses and returned unused pills, which were counted by the BIDMC Research Pharmacy. Physical exams were performed and data on general health status using the 12-Item Short Form Health Survey (SF12) were collected at the initial and final visits. Two study physicians without participant contact (SMB, MAM), reviewed laboratory results to assure safety monitoring while preventing unintentional unblinding of other co-investigators.

Intervention

After completion of the 12-week baseline period, eligible participants were randomized to receive either simvastatin 20 mg tablets twice daily plus vitamin D3 1000 international units capsules twice daily or matching placebo tablets twice daily plus placebo capsules twice daily. Simvastatin was obtained through the BIDMC research pharmacy and was the same generic formulation dispensed within our hospital for clinical care. Vitamin D3 was purchased from Trader Joe's in Brookline, Massachusetts, and was obtained from one manufactured batch and lot. Placebo tablets and capsules matching simvastatin tablets and vitamin D capsules were manufactured by Nutricap Labs (Farmingdale, NY), and contained similar excipients as the statin and vitamin D, but had no active ingredients.

Primary and Secondary Outcomes

The primary outcome was the change in number days with migraine from the baseline period (weeks -12 to 0) to each follow-up period (weeks 1-12 and weeks 13-24) between the placebo and active drug groups. As a non-prespecified outcome, we also evaluated the responder rate, defined as the proportion of participants who had ≥50% reduction in days with migraine from baseline period to the follow-up periods. This outcome was added prior to beginning analysis of our data to better facilitate comparisons to other migraine preventive studies.

Secondary outcomes evaluated the effect of simvastatin plus vitamin D, compared to placebo, on changes from the baseline period to each follow-up period for the number of days and doses of acute migraine medications used, and migraine disability, duration, intensity, and associated symptoms. These outcomes were planned in our original IRB protocol submission.

Sample Size

Based on our prior studies involving migraine patients, we estimated participants would have an average of 8 migraine days/month, with a standard deviation of 4. Assuming a drop-out rate of 25%-50% post-randomization, our goal was to randomize 40 participants to treatment and 40 participants to placebo to achieve 89%-97% power to detect a reduction of 4 migraine days between the active and placebo groups. Ultimately, 89 participants were

enrolled before recruitment was stopped to assure participant completion prior to expiration of the vitamin D and placebo. The decision to stop recruitment was made without examining data.

A post-hoc analysis, based on the actual sample (intervention group: n=28; placebo group: n=29) for the projected effect size (effect size, d=0.89), yielded a power of 85% (α=5%).

Statistical Methods and Analysis

Analyses were conducted by RRN using IBM SPSS Statistics version 19 (IBM Corp., Armonk, NY, USA), SAS version 9.2 (SAS Institute, Inc, Cary, North Carolina) and STATA (StataCorp, College Station, TX) on an intention-to-treat analyses, using all randomized participants.

Within-group differences in days with migraine from the baseline period (weeks -12 to 0; i.e., 84 days) to the follow-up periods (weeks 1-12 and weeks 13-24 post-randomization, 84 days each) were calculated. Between-group differences from the baseline period to each follow-up period were compared between the active drug and placebo group using non-parametric Wilcoxon rank-sum tests. Secondary regression analyses were used to compare the differences between the active and placebo groups, controlling for potential confounders. For the responder rate, the proportion of participants in the active and placebo groups who demonstrated a reduction of ≥50% migraine days from the baseline period to the follow up periods were compared using the Fisher exact test.

Secondary outcomes were compared using Wilcoxon rank-sum tests. We performed pre-planned subgroup analyses stratifying participants by baseline headache days (< or ≥8 per month). Statistical significance was set at $P \leq 0.05$ (two-tailed).

To account for missing data we performed multiple imputation in STATA using “mi impute mvn” which uses multivariate normal data augmentation to impute missing values of continuous imputation variables.[46] Analyses of 20 data sets were performed. In addition, we conducted per protocol analyses (without imputation of missing data) on the primary outcomes, including only participants who completed the full 36 weeks of the study and had at least 80% adherence with study tablets and capsules. Finally, success of blinding was analyzed weeks 12 and 24 post-randomization using the James Blinding Index and Bang's Blinding Index for each arm.

Results

Enrollment and Baseline Measures

Flow of participants through the trial is shown in Figure 1. Of 229 individuals assessed by phone, 140 (61%) were ineligible or did not wish to participate. Of 89 potentially eligible participants who consented, 57 (64%) completed baseline headache diaries and were randomly assigned to simvastatin plus vitamin D (n=28) or matching placebo tablets plus capsules (n=29). Among those randomized, 57 (100%) participated for 24 weeks (12 weeks post-randomization) and 52 (91%) completed the full 36 weeks (24 weeks post-randomization) of the study.

Baseline characteristics of the participants by randomization group were similar at baseline, with the exception of body mass index, which was lower in the active treatment group, age which was older in those assigned to active treatment compared to placebo and baseline number of days with migraine, which was higher in those assigned to active treatment compared to placebo (Table 1). Additional baseline headache characteristics and details on prior migraine therapies used are described in Supplementary Table 1 and were comparable in both groups.

Primary Outcome

Compared to the placebo group, the active treatment group demonstrated a significantly greater decrease in the number of migraine days from the baseline period (weeks -12 to 0) to follow-up period weeks 1-12: -8.0 (IQR: -15.0 to -2.0) days in the active treatment group versus a change of +1.0 (IQR: -1.0 to +6.0) days in the placebo group, P<0.001 (Table 2). Similarly, there was a significantly greater decrease in the number of migraine days in the active treatment group compared to the placebo group from the baseline period to follow-up period weeks 13-24: -9.0 (IQR: -13 to -5) days in the active treatment group versus a change of +3.0 (IQR: -1.0 to +5.0) days in the placebo group, P<0.001.

Responder Rate

A significant association was observed between the study groups (active treatment versus placebo) and the responder rate. Seven of 28 participants (25%) in the active group and one of 29 participants (3%) in the placebo group experienced ≥50% reduction in migraine days (P=0.06) by 12 weeks post-randomization; and eight of 28 participants (29%) in the active group and one of 29 participants (3%) in the placebo group experienced ≥50% reduction in migraine days (P=0.03) by 24 weeks post-randomization.

Secondary Outcomes

Compared to participants taking placebo, those randomized to active treatment used abortive migraine medications significantly fewer days and used significantly fewer doses during both treatment periods compared to the baseline period (Table 2). Migraine disability demonstrated a significantly greater decrease from the baseline period to the treatment period weeks 1-12 (P=0.02), but not to treatment period 13-24 (P=0.08). Symptoms associated with migraine did not change substantially in either group during the study. Specifically, when migraines occurred, no significant changes were seen in migraine severity, migraine duration, or in the proportion of migraines that occurred with throbbing, photophobia, nausea and/or muscular pain.

Regression analyses adjusting for baseline differences

Regression models comparing the differences between the active treatment and placebo groups in the change of number of migraine days, medication use, and migraine disability from the baseline to each follow-up periods are shown in Table 3. Crude (unadjusted) analyses and three adjusted models were performed to adjust for baseline values or scores, as well as age and body mass index, which differed at baseline. These regression models indicated a significant decrease in the number of migraine days in the active treatment group

compared to the placebo group (P<0.001), independent of participants' baseline scores/values, age or body mass index.

Per Protocol Analyses

The results of per-protocol analyses, including only those who completed all 36 weeks of the study, showed similar results to those in Table 2 with imputed data. In per-protocol analyses (complete cases) the regression analyses adjusted for all baseline differences showed the difference in change between the groups to be -9.4 fewer days in the active treatment group compared to the placebo group after 12 weeks of treatment (p<0.001) and -9.7 fewer days in the active treatment group compared to the placebo group after 24 weeks of treatment (p<0.001).

Subgroup Analyses According to Baseline Number of Migraine Days < or ≥8/month

Subgroup analyses in participants with an average of <8 migraine days/month during the baseline period showed significant decreases in days with migraine in the active group during both treatments periods compared to no change in the placebo group (Table 2). Among participants with ≥8 migraine days/month during the baseline period, participants in the active treatment group also had significant reductions in days with migraine during both treatment periods. In contrast, participants assigned to placebo had significant within-group increases in the number of migraine days at each follow up (Table 2).

Adherence and Blinding

All 57 participants (100%) returned migraine diaries for 24 weeks of the study (12 weeks post-randomization). Twenty-four of 28 participants (86%) in the active group and 28 of 29 (97%) in the placebo group completed all 36 weeks of the study (24 weeks post-randomization). Within and between group differences in use of migraine prophylactic agents were not statistically different. Data on stability of migraine medication use and adherence to the intervention during the study are shown in Supplementary Table 2. The types and doses of medications used for migraine preventive and abortive treatments remained generally stable for both groups throughout the study. There were no significant changes in participants' global mental or physical general health (SF12 scores), body mass index, blood pressure, serum glucose, non-migraine body pain (BPI scores), or physical activity duration or intensity. There were no significant between-group differences in changes in major diet components. Calcium intake in each group at baseline was similar (active group: 783 mg/day, IQR: 642-1201 mg/day vs. placebo group: 847 mg/day, IQR: 671-1061 mg/day) and remained stable throughout the study. Magnesium intake declined significantly in the active treatment group from the baseline period to the final period (baseline: 295 mg/day, IQR: 230-389 mg/day vs. intervention weeks 13-24: 253 mg/day, IQR: 214-294 mg/day, P= 0.03) and non-significantly declined in the placebo group (baseline: 285 mg/day, IQR: 212-315 mg/day vs. intervention weeks 13-24: 251 mg/day 208-296 mg/day, P=0.15), but there were no significant between-group differences. Dietary caffeine intake fluctuated from the baseline period in the active treatment group during intervention weeks 1-12 and in the placebo group during intervention weeks 13-24; however, between-group differences were not statistically significant.

Adherence to treatment was good throughout the study with at least 80% of the pills and capsules used by 89% of participants in the active group and 93% in the placebo group during intervention weeks 1-12 and by 96% and 93% in the active and placebo groups, respectively, during intervention weeks 13-24. All but one participant in the study used at least 70% of the pills and capsules throughout the study. Adherence by pill count and report was supported by objective measures of decreased serum LDL-cholesterol (P<0.001) and increased 25 (OH)D (P=0.008) in the active group, and stability of these measures in the placebo group (Supplementary Table 2).

Assessment of participants' blinding at weeks 12 and 24 post-randomization are summarized in Table 4. The James' blinding index is consistent with success of blinding overall, and Bang's blinding indices demonstrate success of blinding for both active and placebo arms.

Adverse events and possible side effects

During the treatment phase, one serious adverse event resulted in investigators withdrawing and unblinding a single participant in the placebo group who had a creatine kinase of 37,780 IU/L. On inquiry, the participant had been vigorously exercising while taking multiple stimulant-containing dietary supplements. The participant experienced full recovery. Other reported side effects or adverse events were mild or transient and were adjudicated to be unlikely due to treatment (Table 4).

Discussion

Use of simvastatin plus vitamin D resulted in a significant decrease in days with migraine at 12 and 24 weeks following randomization compared to placebo. Simvastatin plus vitamin D was also associated with a significantly higher responder rate, and a reduction in days and doses of abortive migraine medications used.

The majority of participants in this study had suffered from migraine attacks for over 10 years, and had previously tried a median of 3 prior abortive agents for migraine. About half of participants had tried, or currently used, a migraine preventive medication. While continuing baseline standard of care treatment for migraine, those receiving treatment with simvastatin 20 mg twice daily plus vitamin D 1000 international units twice daily had a significant reduction in days with migraine per 84-day period of about 9 days, translating to about 3 fewer migraine days per month (30% reduction). Of those in the active treatment group, 29% experienced a ≥50% reduction in days with migraine. In contrast, those continuing standard of care treatment for migraine who received placebo experienced no significant change in migraine days, and had a responder rate of only 3%.

The effect size of 30% fewer migraine days is a magnitude of reduction in migraine days that exceeds the effect of other agents considered to be clinically significant for migraine prevention.[47] Comparisons between other medications used for migraine prevention are challenging due to differences in study designs. For example, in combined analysis, the average responder rate for topiramate 50-200 mg/d was 47%, while the responder rate in the placebo group was 23%, suggesting some placebo effects were possible in both groups.[47] Distinct differences in our study compared to most prior studies include a longer baseline

data collection period (12 weeks versus 4 weeks), and continuation of usual prophylactic migraine medications throughout the study.

Longer collection of baseline data likely allowed for greater stability in baseline parameters. This has an advantage over use of shorter baselines, which may reflect temporarily higher migraine frequencies if individuals are more likely to participate in a migraine study when their migraine attacks are increased from their usual baseline, and may allow time for components of the placebo effect associated with interaction/attention from investigators to wane prior to randomization. Additionally, allowing participants to continue use of their prophylactic migraine medications reduced the possibility that migraine days would increase during the baseline period as a result of stopping a medication preventing headaches. Alternatively, the small placebo effect we observed in this study, compared to placebo responses commonly seen in migraine studies, may be due to negative expectations associated with statins and muscle aches.[48] Myofascial tenderness is more prevalent among individuals with primary headache disorders, including migraine,[49] and is cited as a migraine trigger by many. Participants' expectations that they might experience greater muscle tenderness while using a statin could lead to a reduction in effects attributed to placebo.[50]

Although not statistically significant, use of preventive migraine medications was more common in those randomized to active treatment versus placebo (61% vs. 45% at baseline and 54% vs. 43% at the final visit). In addition to minimizing changes to migraine frequency when preventive medications are stopped prior to participating in a study, allowing use of current preventive medications may have helped prevent dropouts during our study. It is important to note that within the active group, both participants using other prophylactic medications and those using none experienced reduction in migraine frequency with use of simvastatin plus vitamin D therapy.

This study was not powered to detect differences in adverse event rates. However, no serious adverse effects due to treatment occurred; possible side-effects were similar in both active and placebo groups; and participants tolerated and demonstrated good adherence with use of simvastatin plus vitamin D. This contrasts with agents commonly used for migraine prophylaxis, which have frequent side effects/unintentional effects and are often discontinued due to low tolerability (discontinuance rates in clinical trials for amitriptyline, topiramate, and propranolol are 45%, 43%, and 23%, respectively, by 16-26 weeks[11]).

Although these findings are promising, replication in a larger and more diverse population is needed. Participants in this study were balanced at enrollment with respect to numerous characteristics, co-morbidities, and multiple migraine features. However, days with migraine recorded in diaries maintained during the 12-week baseline period prior to randomization showed a statistically significant difference between the groups. This difference was addressed, in part, by pre-planned subgroup analyses, which demonstrated beneficial effects of simvastatin plus vitamin D in both those with a lower migraine burden (<8 migraine days/month at baseline) and those with high migraine burden (≥8 migraine days/month). Although these analyses should be interpreted with caution given small subgroup samples, reductions among those with high migraine burden, which can be more challenging to treat,

were evident. In addition to pre-planned subgroup analyses, we added post-hoc regression analyses to control for differences in the number of migraine days recorded during the baseline period, as well as age and body mass index, which differed at baseline; effect estimates for the models were comparable when these factors were included. This suggests that differential characteristics between the groups at baseline are unlikely to have caused substantial confounding or regression to the mean for the outcomes, and therefore are unlikely to negate the beneficial effect of simvastatin and vitamin D for migraine prevention. Lastly, this design could not distinguish between an effect of simvastatin alone, versus vitamin D alone, versus the combination. A future factorial experiment is required to answer this important clinical and mechanistic question.

In summary, this is the first double-blind placebo-controlled randomized trial evaluating simvastatin 20 mg twice daily plus vitamin D 1000 international units twice daily for prevention of episodic migraine. The results demonstrate that this therapy reduces the number of days with migraine and use of abortive medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Potential Conflicts of Interest: Beth Israel Deaconess Medical Center, Dr. Buettner and Dr. Burstein have applied for a patent for the combination of statin and vitamin D as a prophylactic treatment for migraine. Dr. Buettner has received research funding from Depomed. Dr. Burstein has received funding from the NIH, Merck, Allergan and GlaxoSmithKline and Depomed.

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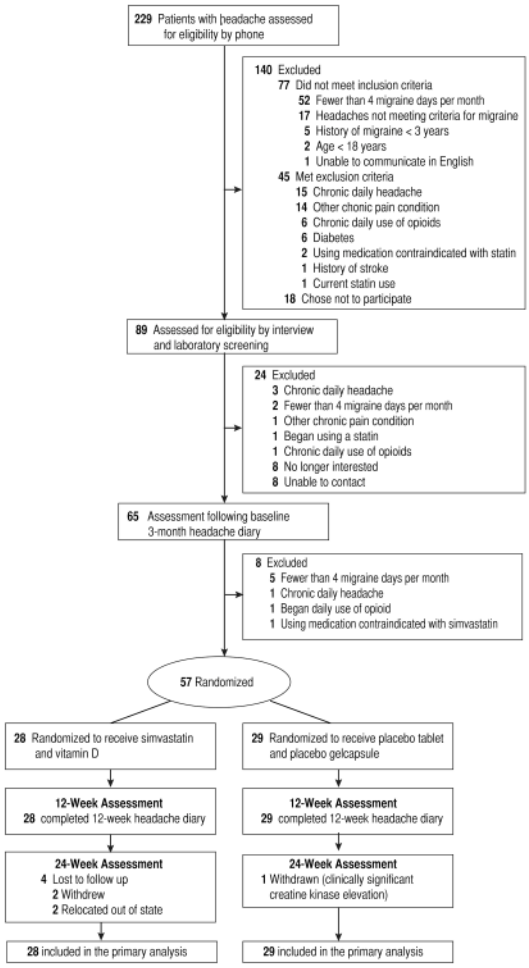

Figure 1.
Flow of participants through the trial.

Table 1
Baseline Demographic and Clinical Characteristics of the Active and Placebo Groups

Characteristics	Active (n = 28)	Placebo (n = 29)	P Value
Age, median (IQR), y	40 (23 to 46)	28 (21 to 34)	0.05
Women, No. (%)	27 (93)	25 (90)	0.61
Non-Hispanic White Race/Ethnicity, No. (%)	24 (86)	21 (72)	0.23
Employment status, No. (%)			0.20
Employed or student	23 (82)	26 (90)	
Homemaker	3 (11)	0 (0)	
Unemployed	2 (7)	3 (10)	
Body mass index, median (IQR)	24.0 (21.8 to 25.4)	26.9 (24.0 to 29.7)	0.03
Smoking status, No. (%)			0.99
Never	23 (82)	24 (83)	
Former	4 (14)	4 (14)	
Current	1 (4)	1 (3)	
Co-morbidities, No. (%)			
Seasonal allergies	10 (36)	14 (48)	0.33
Depression	6 (21)	8 (28)	0.59
Anxiety	4 (14)	6 (21)	0.53
Asthma	4 (14)	2 (7)	0.36
Raynaud's	1 (4)	3 (10)	0.32
Migraine characteristics			
Recorded migraine days/past 3m, median (IQR)	25.5 (14.5 to 34.0)	18.0 (14.0 to 23.0)	0.05
Migraine usually starts unilaterally, No. (%)	21 (75)	25 (86)	0.28
Throbbing migraine pain, No. (%)	22 (79)	24 (83)	0.69
Photophobia	27 (96)	28 (97)	0.98
Phonophobia	23 (82)	26 (90)	0.41
Nausea	23 (82)	24 (83)	0.95
Current non-migraine medications/supplements			
Allergy medication	5 (18)	4 (14)	0.67
Anti-depressant/anti-anxiety medication	1 (4)	4 (14)	0.17
Estrogen contraception/hormone replacement	10 (36)	16 (55)	0.14
Other non-migraine medication (s)	3 (11)	3 (10)	0.96
Multivitamin	11 (39)	9 (31)	0.51
Calcium supplement	6 (21)	2 (7)	0.11
Other non-migraine dietary supplement (s)	13 (46)	10 (34)	0.36
Current use of a migraine preventive medication	17 (61)	13 (45)	0.23
Number of prior migraine abortive therapies tried and not currently using, median (IQR)	3 (1 to 3)	3 (2 to 4)	0.20
Number of prior migraine preventive therapies tried and not currently using, median (IQR)	1.5 (0.5 to 3.5)	1.0 (0 to 3)	0.79

Table 2

Change Within Groups and Between Group Comparisons for Number of Migraine Days, Medication Days, Medication Doses, and Disability

	Number/12-Week Period Median (IQR)						Change Within Groups[a,b] Median (IQR)				P Value for Change Between Groups[c]	
Period:	**Baseline Weeks -12 to 0**		**Intervention Weeks 1-12**		**Intervention Weeks 13-24[d]**		**Intervention Weeks 1-12**		**Intervention Weeks 13-24[d]**		**Weeks 1-12**	**Weeks 13-24[d]**
Outcome	**Active n=28**	**Placebo n=29**	**Active n=28**	**Placebo n=29**	**Active n=28**	**Placebo n=29**	**Active n=28**	**Placebo n=29**	**Active n=28**	**Placebo n=29**		
No. of days with migraine	25.5 (14.5 to 34.0)	18.0 (14.0 to 23.0)	18.0 (8.0 to 24.0)	17.0 (14.0 to 26.0)	16.5 (10.0 to 23.5)	18.0 (15.0 to 24.0)	-8.0 (-15.0 to −2.0) p<0.001	1.0 (-1.0 to 6.0) p=0.23	-9.0 (-13.0 to −5.0) p<0.001	3.0 (-1.0 to 5.0) p=0.06	p<0.001	p<0.001
No. of days used abortive medication	20.5 (14.0 to 27.5)	16.0 (11.0 to 21.0)	14.0 (6.0 to 20.5)	14.0 (8.0 to 21.0)	16.0 (9.0 to 20.0)	14.0 (10.0 to 24.0)	-4.5 (-11.0 to −1.0) p<0.001	-1.0 (-3.0 to 1.0) p=0.56	-7.0 (-12.0 to 0.0) p<0.001	2.0 (-3.0 to 2.0) p=0.45	p=0.002	p<0.001
No. of doses of abortive medication	24.5 (14.5 to 31.5)	19.0 (14.0 to 16.0)	14.0 (8.0 to 24.5)	17.0 (11.0 to 27.0)	16.5 (9.5 to 21.0)	18.0 (12.0 to 25.0)	-5-5 (-13.5 to −5.0) p<0.001	-2.0 (-7.0 to 4.0) p=0.20	-7.0 (-15.0 to −3) p<0.001	0.0 (-7.0 to 3.0) p=0.70	p=0.05	p=0.004
Migraine Disability (MIDAS)	21.5 (8.0 to 40)	16.0 (9 to 29)	10 (5 to 19)	10 (3 to 43)	12 (3 to 18)	15 (4 to 27)	-13.0 (−22.7 to −1.0) p<0.001	-4.0 (−8.0 to 3.0) p=0.12	-8.0 (−31.9 to −1.0) p=0.002	-4.0 (−14.0 to 8.0) p=0.36	p=0.02	p=0.08
Subgroup analyses: Baseline migraines <8 per month[e]												
No. of days with migraine	14.0 (13.0 to 22.0)	16.5 (14.0 to 19.0)	8.0 (6.0 to 13.0)	15.0 (13.0 to 18.0)	10.0 (4.0 to 16.0)	17.0 (15.0 to 19.0)	-4.0 (-8.0 to −2.0) p=0.002	-0.5 (-4.0 to 3.0) p=0.92	-5.0 (-9.0 to −2.0) p=0.02	0.5 (-3.0 to 4.0) p=0.45	p=0.007	p=0.006
Subgroup analyses: Baseline migraines ≥8 per month[f]												
No. of days with migraine	34.0 (28.0 to 38.0)	26.0 (24.0 to 43.0)	24.0 (19.0 to 29.0)	34.0 (27.0 to 44.0)	23.0 (16.0 to 26.0)	34.0 (29.0 to 46.0)	-11.0 (-15.0 to −3) p=0.002	7.0 (2.0 to 10.0) p=0.02	-12.0 (-15.0 to −8.0) p<0.001	5.0 (3.0 to 9.0) p=0.03	p<0.001	p<0.001

Abbreviation: IQR, interquartile range; CI, confidence interval, MIDAS, migraine disability assessment questionnaire

[a] A negative change within groups means improvement during the 12-week period compared to baseline.

[b] P values were calculated using Wilcoxon signed-rank test.

[c] P values were calculated using a two-sample Wilcoxon rank-sum test.

[d] Missing data for weeks 13-24 were multiply imputed for 4 participants in the active arm and 1 participant in the placebo arm.

[e] Subgroup Active n=13 and Placebo n=22.

[f] Subgroup Active n=15 and Placebo n=7.

Table 3

Unadjusted and Adjusted Modeling of Difference in Change Between Groups[a] for Days with Migraine, Days Used Abortive Medications, Doses of Medication Used, and Migraine Disability Score

	Difference in Change Between Groups			
	Unadjusted Model[b]	**Adjusted Model 1[c]**	**Adjusted Model 2[d]**	**Adjusted Model 3[e]**
Intervention Weeks 1-12 Compared to Baseline				
No. of days with migraine	-9.8 (-13.5 to -6.0) p<.001	-9.4 (-13.4 to-5.5) p<.001	-10.0 (-14.1 to -6.0) p<.001	-9.9 (-14.2 to -5.7) p<.001
No. of days used abortive medication	-5.9 (-9.1 to -2.7) p=.001	-5.4 (-8.7 to -2.1) p=.002	-6.1 (-9.4 to -2.7) p=.001	-6.3 (-9.9 to −2.8) p<0.001
No. of doses of abortive medication	-5.1 (-9.4 to -0.7) p=0.02	-4.7 (-9.0 to -0.5) p=0.03	-5.8 (-10.1 to -1.4) p-0.01	-5.8 (-10.3 to −1.3) p=0.01
Migraine Disability (MIDAS)[f]	-10.8 (-22.0 to 0.4) p=0.06	-10.7 (-19.4 to -2.1) p=0.02	-10.2 (-19.2 to -1.1) p=0.03	-9.7 (−19.6 to -0.2) p=0.05
Intervention weeks 13-24[g] Compared to Baseline				
No. of days with migraine	-10.2 (-13.4 to -7.0) p<.001	-9.3 (-12.5 to -6.0) p<.001	-9.8 (-13.1 to -6.4) p<.001	-10.2 (-13.7 to- 6.7) p<.001
No. of days used abortive medication	-7.2 (-10.5 to -4.0) p<.001	-6.4 (-9.6 to -3.1) p<.001	-7.1 (-10.3 to -3.8) p<.001	-7.4 (-11.0 to −4.0) p<0.001
No. of doses of abortive medication	-7.7 (-12.5 to -2.8) p<0.002	-7.1 (-11.5 to -2.7) p=.002	-8.4 (-12.8 to -4.0) p<.001	-8.9 (-13.5 to −4.3) p=0.001
Migraine Disability (MIDAS)	-11.8 (-25.3 to 3.2) p=0.13	-11.0 (-21.0 to -1.0) p=0.03	-12.5 (-23.0 to -2.2) p=0.02	-12.0 (−22.9 to -1.1) p=0.03

Abbreviations: MIDAS, Migraine Disability Assessment Questionnaire

[a] The difference in change was calculated as change from baseline (weeks -12 to 0) in active group minus change in placebo group. A negative difference in change between groups favors the active group.

[b] Results from regression analyses unadjusted for other factors.

[c] Model 1: Adjusted for baseline values/scores.

[d] Model 2 Adjusted for baseline values/scores and age.

[e] Model 3: Adjusted for baseline values/scores, age, and body mass index.

[f] Missing data for weeks 1-12 were multiply imputed for 3 participants in the active arm.

[g] Missing data for weeks 13-24 were multiply imputed for 4 participants in the active arm and 1 participant in the placebo arm.

Table 4
Adverse effects/side effects and success of blinding

Measure	Intervention Weeks 1-12		Intervention Weeks 13-24	
	Active (n=28)	Placebo (n=29)	Active (n=24)	Placebo (n=28)
Side effects/adverse events[a], No. (%)	2 (7)	6 (21)	3 (12)	6 (21)
Abdominal/gastrointestinal symptoms	0 (0)	1 (4)	0 (0)	2 (7)
Joint or skeletal pain	0 (0)	1 (4)	1 (4)	2 (7)
Myalgia (without CK elevation)	0 (0)	2 (7)	1 (4)	1 (4)
Myositis (clinically significant CK)	0 (0)	1 (4)	0 (0)	0 (0)
Skin rash or itch	2 (7)	1 (4)	1 (4)	1 (4)
Blinding questionnaire responses [b], No. (%)				
“I strongly believe I am taking the statin and vitamin D”	5 (20)	1 (4)	5 (21)	2 (7)
“I somewhat believe I am taking the statin and vitamin D”	4 (16)	7 (24)	5 (21)	5 (18)
“I don’t know”	12 (48)	12 (41)	7 (29)	13 (46)
“I somewhat believe I am taking the placebo”	1 (4)	4 (14)	4 (17)	6 (22)
“I strongly believe I am taking the placebo”	3 (12)	5 (17)	3 (12)	2 (7)
James Blinding Index (95%CI)	0.66 (0.56 to 0.77)[c]		0.65 (0.55 to 0.76)[c]	
Bang's Blinding Index for active arm (95%CI)	0.20 (-0.03 to 0.43)[d]		0.13 (-0.15 to 0.40)[d]	
Bang's Blinding Index for placebo arm (95%CI)	0.03 (-0.20 to 0.27)[d]		0.04 (-0.19 to 0.26)[d]	

[a] Side effects/adverse events were defined as any new or worsening problem possibly related to treatment.

[b] Blinding questionnaire completed by 25 in active group and all in placebo group at week 12 post-randomization and by 24 in active group and 28 in placebo group at 24 weeks post-randomization.

[c] The James' Blinding Index ranges from 0 to 1, where 0 indicates complete lack of blinding, 1 complete blinding, and 0.5 completely random guessing. A 95%CI completely above 0.50 represents statistically significant blinding beyond chance.

[d] The Bang Blinding Index ranges from −1 and 1, with values closer to 0 representing successful random blinding and values closer to 1 or -1 implying failure in blinding above random guessing or opposite guessing, respectively.