Annals of Internal Medicine | ORIGINAL RESEARCH

N-of-1 (Single-Patient) Trials for Statin-Related Myalgia

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Background: Statin-related myalgia is difficult to distinguish from other conditions causing myalgia and may often lead to statin discontinuation.

Objective: To compare the effect of statin rechallenge with placebo in patients with prior statin-related myalgia and to determine whether patients resumed statin therapy after evaluating the results.

Design: *N*-of-1 trial with 3 double-blind, crossover comparisons separated by 3-week washout periods. (Clinicaltrials.gov: NCT01259791)

Setting: Tertiary care lipid clinic.

Patients: Patients with prior statin-related myalgia with or without mild elevation of creatine kinase levels.

Intervention: Rechallenge with the statin that was previously associated with myalgia within 3 weeks of open-label use versus matching placebo.

Measurements: Weekly visual analogue scale (VAS) scores for myalgia and specific symptoms (VAS myalgia score and symptom-specific VAS score, respectively), pain interference scores, and pain severity scores were recorded during the 3-week periods when patients were receiving placebo or statin. The primary outcome was the VAS myalgia score (range, 0 to 100 mm).

Results: Eight patients (mean age, 66 years [SD, 8 years]; 88% women, all with high 10-year Framingham cardiovascular risk) participated in *n*-of-1 trials. Seven patients completed 3 treatment pairs, and 1 completed 2 treatment pairs. For each *n*-of-1 trial, no statistically significant differences were seen between statin and placebo in the VAS myalgia score, symptom-specific VAS score, pain interference score, and pain severity score. Five patients resumed open-label statin treatment, with a median posttrial follow-up of 10 months.

Limitation: Results are limited by the small sample size and cannot be extended to patients with longer onset of myalgia after statin initiation.

Conclusion: In selected patients with a history of statin-related myalgia whose symptoms are difficult to evaluate, *n*-of-1 trials may be a useful method for determining statin tolerability.

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Statin-related myopathy is an umbrella term that includes patients with myalgia (muscle symptoms without creatine kinase [CK] elevation), myositis (muscle symptoms with CK elevation), and rhabdomyolysis (1). Although older randomized clinical trials have shown the incidence of muscle symptoms with clinically significant CK elevations to be low (1% to 5%) (2, 3), recent trials have reported the incidence of statin-related muscle symptoms regardless of CK levels to be as high as 15% to 20% (4, 5). Thus, statin-related myopathy is common and is an important problem because it may lead to patients discontinuing a therapy that has been shown to improve cardiovascular outcomes.

The diagnosis of statin-related myalgia in most patients is not optimum because there is no highly specific diagnostic test. Creatine kinase levels are usually normal or only slightly increased (6). Moreover, myalgia and changes in CK levels can often occur for other reasons, including physical exertion and fibromyalgia (7). Muscle biopsies are invasive and may not be congruent with symptoms or CK elevations (8, 9). Thus, the diagnosis of statin-related myalgia is primarily dependent on patients' and physicians' impressions of causality during open-label statin therapy. This approach can lead to false conclusions that statins cause myalgia because of inherent biases in unblinded, before–after therapeutic trials (10). *N*-of-1 trials (single-patient, randomized, multiple crossover, blinded comparisons of an active treatment vs. placebo) are the most effective way to limit these biases in individual patients because each patient serves as his or her own control (11). These trials have been used to optimize management for many chronic problems, including those associated with pain (12), but they have not been used for statin-related myalgia.

We therefore conducted a proof-of-concept study to assess the feasibility and potential value of *n*-of-1 trials in patients with statin-related myalgia. We hypothesized that such trials would yield objective proof in some patients that their symptoms were (or were not) statin-related. We also assessed patients' willingness to resume statin therapy after completion of their respective trials.

METHODS

Design Overview

Design of the *n*-of-1 trials was consistent with previously published guidelines (13). Each trial lasted up to 33 weeks and comprised a maximum of 3 statin and placebo

See also:

Print
Summary for Patients I-34

Context

Differentiating statin-related myalgia from myalgia due to other causes can be difficult and largely relies on subjective responses to open-label cessation or reinstitution of therapy.

Contribution

In this proof-of-concept study, patients previously reporting symptoms while receiving statins had several pairs of double-blind statin or placebo challenges (*n*-of-1 trials). None of the patients had a statistically significant difference in myalgia or other pain measures during statin therapy compared with placebo, and most resumed statin therapy after reviewing their results.

Implication

N-of-1 trials are a feasible and potentially useful tool to examine myalgia during statin rechallenge in selected patients.

—The Editors

treatment pairs assigned in random order (**Figure 1**). Because we only included patients who had previously developed myalgia within 3 weeks of open-label statin use (see Setting and Participants), we used 3-week treatment periods (statin or placebo) to allow for adequate time for myalgia to develop. For each patient, the specific statin and daily dose that had previously been associated with the development of myalgia were used in the respective *n*-of-1 trial.

Treatment periods were separated by 3-week washout intervals to minimize carryover effects (13, 14). The duration was substantially longer than the washout of 100 hours measured for the statins (rosuvastatin and atorvastatin) with the longest half-lives (15 to 20 hours) (15) because some patients may report slower resolution of symptoms than predicted by pharmacokinetics (16). If patients developed symptoms, they were offered the option of discontinuing a treatment period early and crossing over to the other treatment period after a washout period. The trial could be stopped and the treatment assignment unblinded at any point if the patient was convinced that a clear difference had emerged between treatment periods.

The order of the statin or placebo was randomly allocated within pairs according to a computer-generated list held by the hospital pharmacist, who had no contact with patients. Randomization was done by using the Web site www.randomizer.org, which generates a set of random numbers. A total of 30 sets of random numbers (numerals 1 [arbitrarily designated as placebo] or 2 [designated as active]) were generated for a total of 10 patients. We then used 3 of these sets per patient. Blinding was maintained by use of identical-looking dispensing bottles and capsules in which statin or placebo pills were compounded by the hospital pharmacy. Physicians and all other study personnel were blinded to the drug sequence.

Setting and Participants

We recruited patients aged 18 years or older through advertisements and from endocrinology clinics at a tertiary referral center. Patients were included if they had a history of hypercholesterolemia requiring statin therapy according to the Canadian Dyslipidemia Guidelines (17) and statin-related myalgia (as defined by the American College of Cardiology [1]) without clinically significant CK elevations (<3 times the upper limit of normal or <3 times the baseline value) occurring within 3 weeks of starting open-label statin therapy. We only included patients who could not tolerate statin therapy. Despite having previously tried and discontinued statin therapy for myalgia, all patients were willing to retry their prior statin. We excluded patients with a history of rhabdomyolysis, metabolic or inflammatory myopathy, or neuropathy and those who could not comply with the added demands of an *n*-of-1 trial. The study was approved by the Western University Research Ethics Board, and all participants provided informed consent.

Outcomes and Follow-up

The baseline visit included a history and physical examination; measurement of serum CK, aspartate aminotransferase, alanine aminotransferase, and creatinine levels; and a set of questionnaires that assessed symptoms of possible myalgia. We also recorded the most recent fasting low-density lipoprotein cholesterol (LDL-C) level that the patient had while not receiving a statin in the past year.

We assessed patients for myalgia by using 2 self-completed visual analogue scales (VASs) and the Brief Pain Inventory (BPI) Short Form (18, 19). One VAS focused on myalgia (VAS myalgia score), and the second assessed a specific symptom identified by the patient as being the most troublesome during prior statin therapy (symptom-specific VAS score). The stem question for the myalgia VAS was, "How severe is your muscle pain today?" The patient-specific symptoms included generalized muscle pain, pain in a particular muscle group, muscle weakness, or muscle cramping. The stem question for the symptom-specific VAS was, "How severe was your [X] today?" in which "X" was replaced with the patient's specific symptom. For both VAS questions, the patient responded by making a mark between 0 mm (no symptoms) and 100 mm (maximum intensity for the symptom in question) on a horizontal line. The BPI is a self-completed, validated measure of clinical pain (20). The pain severity score (PSS) (mean score of questions 3 to 6 of the BPI) and the pain interference score (PIS) (mean score of questions 9A to 9G of the BPI) were calculated (19). The PSS and PIS have scores ranging from 0 to 10, with higher scores indicating worse pain severity and pain interference, respectively.

Patients completed the myalgia VAS, symptom-specific VAS, and BPI at baseline before commencing the

n-of-1 trial. During each 3-week period (statin or placebo), each questionnaire was completed at the end of each week (that is, days 7, 14, and 21) (**Figure 1**). Because longer duration of exposure to statin should theoretically result in greater symptoms, we suspected that symptom intensity would be greatest on the last day of each completed week. A patient completing 3 full treatment pairs in an *n*-of-1 trial provided a total of 18 follow-up questionnaire sets (myalgia VAS, symptom-specific VAS, and BPI). If a patient found symptoms to be intolerable and wished to move to a washout period early, they were instructed to complete their questionnaires when they terminated the treatment period. At the follow-up study visits (weeks 3, 9, 15, 21, 27, and 33), we used pill counts to assess adherence; drew blood for CK, aspartate aminotransferase, alanine aminotransferase, and creatinine levels; recorded adverse events; and collected the questionnaires. Follow-up visits could be moved to earlier points if the treatment periods were terminated early. To maintain blinding, we did not measure serum LDL-C levels during the *n*-of-1 trials.

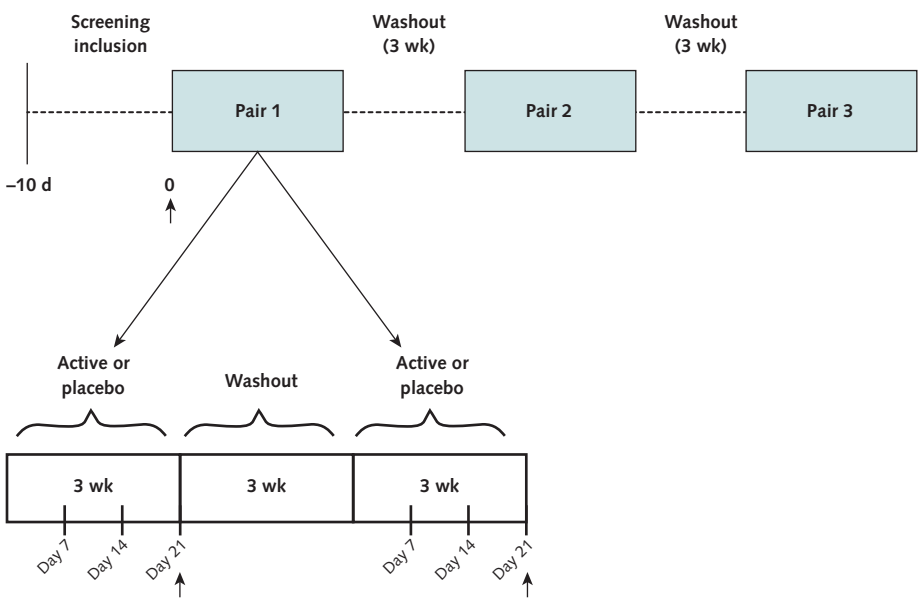
At the conclusion of each *n*-of-1 trial, unblinded results of the VAS myalgia score, symptom-specific VAS score, PSS, and PIS were reviewed with the patient by the *n*-of-1 trial physician. The decision whether to resume a statin was based on this discussion. When the trial physician was not the patient's primary physician for management of hypercholesterolemia, the trial results were conveyed to the patient's primary physician and the decision to resume open-label use of a particular statin was left to the patient and his or her physician. We contacted the patient's primary physician at least 3 months after completion of the trial to obtain follow-up lipid levels and determine whether the patient had resumed a statin.

Statistical Analysis

We analyzed results within each *n*-of-1 trial and combined results across them. The prespecified primary outcome in both analyses was the difference in mean VAS myalgia scores between statin therapy and placebo. A difference of at least 13 mm in the VAS pain score was considered to be clinically significant (21, 22). Secondary outcomes included the mean differences (statin minus placebo) for the symptom-specific VAS score, PSS, and PIS. A change of 1 or more points in the PSS or PIS was considered to be clinically significant (23, 24).

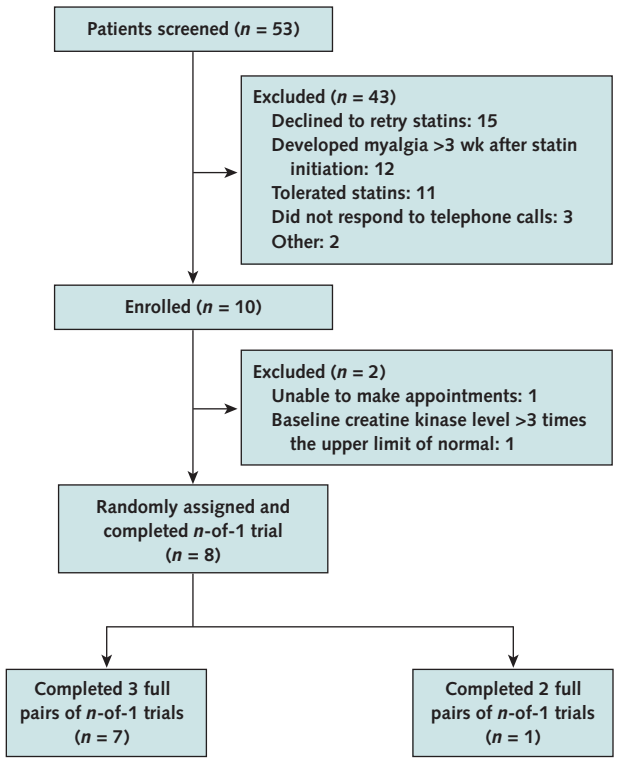
For analyses of individual *n*-of-1 trials, the means and 95% CIs for the differences (statin minus placebo) in symptom scores were calculated within treatment pairs for each outcome (VAS myalgia score, symptom-specific VAS score, PSS, and PIS) by using paired *t* tests. We defined a "positive" *n*-of 1 trial as one that had a higher VAS myalgia score for all completed pairs and a score that was at least 13 mm higher in at least 2 of 3 treatment pairs during statin therapy versus placebo. For the combined analysis across the *n*-of-1 trials, we adapted the mixed-model method for

Figure 1. **Study design.**



The study duration was 33 wk. After the baseline assessment at time 0, patients had 3 pairs of active drug (3 wk) and placebo (3 wk) exposures. Randomly assigned treatment pairs comprised 2 treatment periods (active therapy or placebo) separated by a 3-wk washout period. Treatment pairs were also separated by washout periods. A complete *n*-of-1 trial comprised 3 treatment pairs. Clinic visits occurred at baseline and at the end of each treatment period (*solid arrows*). Baseline scores for the visual analogue scales and Brief Pain Inventories were collected at time 0. Patients then completed these questionnaires at days 7, 14, and 21 in each treatment period.

Figure 2. **Study flow diagram.**



combining *n*-of-1 trials (25). We fitted regression models to each outcome with the treatment indicator as the single explanatory variable. The Kenward–Roger approximation was used to adjust for standard error bias due to the small number of patients. We assumed that the repeated measures followed a first-order autoregressive model, and we accounted for variability among patients by fitting them as random effects. The model we used can be expressed as $y = X\alpha + Z\beta + e$, where vector y is the outcome, matrix X is the design matrix for the fixed effect α, matrix Z is the design matrix for the random effect β, and e is the residue vector. The total variance–covariance matrix V is given by $V = ZGZ^T + R$ where G is a diagonal and R has AR(1) structure. Prestudy and poststudy LDL-C levels were compared by using paired t tests. A P value less than 0.05 was considered statistically significant, and reported P values were not adjusted for multiple comparisons. We used SAS, version 9.3 (SAS Institute, Cary, North Carolina), to conduct the analyses.

The decisions to enroll 10 statin-intolerant patients and to limit each *n*-of-1 trial to 3 treatment pairs were made in advance and were not based on formal power calculations. Because this was a proof-of-concept study, we judged that 10 patients would be sufficient to establish the feasibility of the approach and determine whether *n*-of-1 trials confirmed or refuted an association between statins and myalgia in selected patients. We limited the *n*-of-1 trials to 3 treatment pairs as a tradeoff between less power to detect a true difference in a single patient (in which power is determined by the number of treatment exposures) and the practical need to limit the duration of the trials.

Role of the Funding Source

The funding sources had no influence on study design; data collection, analysis, or interpretation; or the decision to submit the manuscript for publication.

RESULTS

Participant Flow and Baseline Characteristics

Of 53 patients screened for participation, 10 were eligible for the study and completed the baseline visit; 2 withdrew before commencement, and 8 started their *n*-of-1 trial (**Figure 2**). One patient completed the first pair of treatments but was hospitalized emergently for diverticulitis at the time of her second follow-up visit. Data from her first treatment pair were discarded, and after recovery, she restarted the *n*-of-1 trial and completed 3 full pairs.

Baseline characteristics are shown in **Table 1**. All patients (mean age, 66 years [SD, 8 years]) were at high cardiovascular risk based on the Framingham score (10-year risk ≥20%). Their mean baseline LDL-C value was 3.30 mmol/L (128 mg/dL) (SD, 1.54 mmol/L [60 mg/dL]). The median number of statins previously tried but discontinued because of myalgia was 3 (range, 1 to 6 statins). Rosuvastatin and atorvastatin were the most common statins previously tried. Baseline VAS, PSS, and PIS values showed that patients had mild baseline pain despite not receiving a statin for at least 3 months before study entry.

Randomization schemes, statin dosing regimens, and adherence for each *n*-of-1 trial are shown in **Table 2**. Overall, pill counts showed 92% adherence among patients. Patients 1 to 7 completed 3 full pairs in the *n*-of-1 trials. Patient 6 crossed over during the second week in the first period (while receiving placebo) because of myalgia but completed the rest of the trial as planned. Patient 8 decided not to complete the final treatment period (active atorvastatin) because of myalgia that developed during the preceding placebo period. Statistical assessment of the *n*-of-1 trial for this patient was therefore based on 2 completed treatment pairs. Patient 7 forgot to complete 1 set of questionnaires during treatment period 6. Otherwise, data collection was complete for all patients.

Outcomes

Table 3 shows the means and 95% CIs for the statin-minus-placebo differences in VAS myalgia score, symptom-specific VAS score, PSS, and PIS. For the primary outcome of the VAS myalgia score, 7 of the 8 patients did not show statistically greater myalgia symptoms during statin treatment versus placebo. Patient 8 met the

prespecified clinically significant difference for the VAS myalgia score but did not attain statistical significance given the wide CIs. Furthermore, this patient resumed statin therapy after the trial. **Figure 3** depicts each patient's VAS myalgia scores according to treatment period in their respective *n*-of-1 trial. For the symptom-specific VAS score, patient 2 showed statistically greater discomfort during statin treatment versus placebo, but the mean difference did not meet the prespecified clinically significant difference of 13 mm. For the remaining secondary outcomes, no patients had statistically significant differences between statin treatment and placebo.

Combined analysis of data from the eight *n*-of-1 trials found no statistically significant differences between statin treatment and placebo for myalgia VAS, symptom-specific VAS, and PIS measurements (**Table 4**). For the PSS, the patients showed statistically greater discomfort during statin treatment versus placebo, but the mean difference did not meet the prespecified clinically significant difference of 1 point (**Table 4**). No statistically significant differences in CK and liver enzyme levels were seen between statin and placebo (data not shown). Two serious but unrelated adverse events occurred in this trial: hospitalization for diverticulitis in 1 patient and a new diagnosis of melanoma in situ requiring excision in another patient.

After the conclusion of the trial, 1 patient's follow-up LDL-C level was below the recommended target and a statin was not resumed. Five of the 7 remaining patients requiring statin therapy resumed and have continued to receive the statin examined in their *n*-of-1 trials to a median follow-up of 10 months (range, 5 to 18 months) (**Table 3**). The decision to resume a statin was associated with an improvement in mean LDL-C level from 3.82 mmol/L (148 mg/dL) (SD, 0.43 mmol/L [17 mg/dL]) to 1.82 mmol/L (70 mg/dL) (SD, 0.56 mmol/L [22 mg/dL]) (P = 0.018), with 4 (80%) of 5 patients achieving LDL-C levels less than 2.0 mmol/L (77 mg/dL).

DISCUSSION

In this proof-of-concept study, we assessed the feasibility and utility of *n*-of-1 trials in patients with statin-related myalgia. We found no clinically significant differences in myalgia or other pain measures in any of the *n*-of-1 trials or in combined results across trials. We also found that most patients resumed their respective statin after reviewing results of their *n*-of-1 trials and that this was associated with lower LDL-C levels 10 months later. Our results suggest that *n*-of-1 trials are a feasible and potentially useful tool to examine myalgia caused by statin rechallenge in selected patients.

Our study has several strengths. Use of randomization and placebo controls in the *n*-of-1 trials limited patient and physician biases that would otherwise tend to associate symptoms with open-label statin use. Similarly, multiple exposures to the statin and placebo helped control for fac-

Table 1. **Baseline Characteristics**

Characteristic	All Patients (n = 8)
Mean (SD) age, *y*	66 (8)
Female, *n (%)*	7 (88)
High Framingham cardiovascular risk, *n (%)*	8 (100)
Diabetes or prediabetes	7 (88)
Coronary artery disease	2 (25)
Median duration of dyslipidemia (range), *y*	7 (1–42)
Median statins tried before study (range), *n*	3 (1–6)
Statins previously tried, *n (%)*	
Rosuvastatin	8 (100)
Atorvastatin	6 (75)
Simvastatin	4 (50)
Pravastatin	3 (38)
Fluvastatin	3 (38)
Lovastatin	2 (25)
Intolerance of nonstatin medications, *n (%)*	
None	4 (50)
Ezetimibe	3 (38)
Fenofibrate	1 (12)
Current lipid-lowering regimen, *n (%)*	
None	3 (38)
Ezetimibe	2 (25)
Fibrate	0 (0)
Niacin or derivative	2 (25)
Bile acid resin	1 (12)
ω-3 fatty acids	1 (12)
Mean (SD) biochemical values	
Total cholesterol level	
mmol/L	5.79 (0.61)
mg/dL	224 (24)
LDL-C level	
mmol/L	3.30 (1.54)
mg/dL	128 (60)
HDL-C level	
mmol/L	1.35 (0.37)
mg/dL	52 (14)
Triglyceride level	
mmol/L	2.27 (1.19)
mg/dL	201 (105)
CK level, *IU/L*	124 (68)
Aspartate aminotransferase level, *IU/L*	28 (9)
Alanine aminotransferase level, *IU/L*	31 (15)
Creatinine level	
μmol/L	76 (16)
mg/dL	0.86 (0.18)
Mean (SD) outcome parameters	
VAS myalgia score, *mm**	14 (13)
Symptom-specific VAS score, *mm**	8 (13)
PSS†	2.9 (1.1)
PIS‡	2.4 (2.8)

CK = creatine kinase; HDL-C = high density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PIS = pain interference score; PSS = pain severity score; VAS = visual analogue scale.
* Higher scores (range, 0–100) indicate greater muscle symptoms.
† Higher scores (range, 0–10) indicate greater symptom severity.
‡ Higher scores (range, 0–10) indicate greater symptom interference.

Table 2. **Summary of Individual *N*-of-1 Trials**

Patient Number	Active Therapy	Symptom for Symptom-Specific VAS	Randomization Sequence	Completed Pairs, *n*	Compliance Rate, %
1	Atorvastatin, 10 mg once daily	Muscle pain	PA-AP-AP	3	97
2	Rosuvastatin, 5 mg once daily	Muscle pain	PA-AP-AP	3	92
3	Pravastatin, 10 mg once daily	Foot pain	AP-PA-PA	3	98
4	Rosuvastatin, 20 mg once daily	Lower back pain	AP-AP-PA	3	98
5	Rosuvastatin, 10 mg once weekly	Calf pain	AP-AP-AP	3	100
6	Rosuvastatin, 5 mg once daily	Muscle cramping	PA-PA-PA	3	100
7	Rosuvastatin, 10 mg once daily	Muscle weakness	AP-PA-AP	3	100
8	Atorvastatin, 10 mg once daily	Muscle cramping	PA-PA-PA	2	100

A = active; P = placebo.

tors other than the statin that caused myalgia. Furthermore, our *n*-of-1 trials had features that made it less likely that we missed detecting adverse effects of statins on patients' symptoms. First, our assessment of patients' muscle symptoms included not only generic pain measures (VAS myalgia score, PIS, and PSS) but also the specific symptom that patients previously associated with statin use (symptom-specific VAS score). Second, we rechallenged patients with the same statin and dose previously believed to have caused their symptoms during open-label use. Third, we primarily included patients with a history of recurrent myalgia after multiple open-label statin challenges. We therefore expected that our patients would be more likely to report myalgia after being rechallenged with a statin that had previously been associated with symptoms, but the *n*-of-1 trials seemed useful in reassuring patients and their physicians that the statin was not the source of muscle symptoms.

Statin-related adverse effects on muscle are a commonly cited reason for discontinuation and can lead to statin withdrawal in patients who would otherwise benefit. A recent retrospective cohort study involving more than 100 000 patients who were prescribed statins in routine practice found that 5495 (5.1%) discontinued use because of muscle symptoms, but a much smaller number discontinued use because of elevated CK levels (>3 times the upper limit of normal) (n = 992 [0.9%]) or rhabdomyolysis (n = 7 [0.006%]) (26). Muscle-related symptoms have been reported as the most common adverse event leading to statin discontinuation (27). The importance of muscle-related adverse effects due to statin use is highlighted by the association between statin discontinuation and a higher risk for cardiovascular events, including death (26, 28, 29). Thus, strategies to improve diagnosis and treatment of statin-related myalgia are needed.

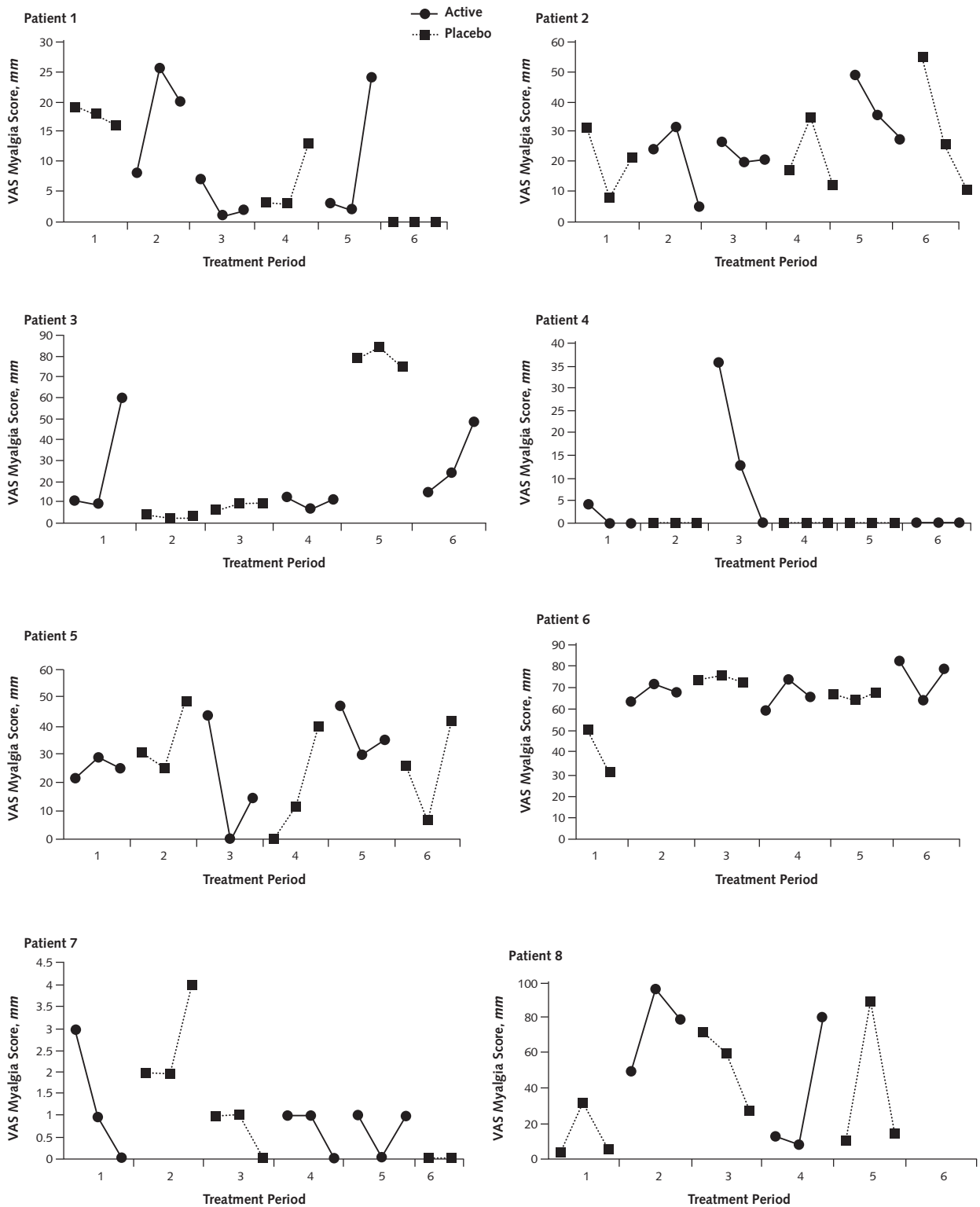
Because statin-related myalgia lacks an objective biomarker or test to accurately differentiate it from myalgia due to other causes, the diagnosis has largely relied on subjective patient responses during and after open-label statin use. Creatine kinase levels are a standard assay for patients with muscle symptoms. However, CK levels may be elevated for other reasons (7) or may be normal despite objective weakness (8). Moreover, the relationship between CK levels and abnormal muscle biopsy results is not consistent (9, 30). These inconsistencies may be partly explained by patients whose muscle-related symptoms are not truly caused by a statin; in such patients, certainty about causality requires comparison of muscle-related symptoms

Table 3. **Differences in Pain Measures During Statin Treatment and Receipt of Placebo in Individual *N*-of-1 Trials**

Patient Number	VAS Myalgia Score, *mm*		Symptom-Specific VAS Score, *mm*		PSS		PIS		Resumed Statin After Completing *N*-of-1 Trial
	Mean (95% CI)*	*P* Value	Mean (95% CI)*	*P* Value	Mean (95% CI)*	*P* Value	Mean (95% CI)*	*P* Value	
1	2.3 (−14.0 to 18.6)	0.60	1.9 (−16.6 to 20.4)	0.70	1.0 (−1.2 to 3.2)	0.187	0.5 (−1.3 to 2.4)	0.35	Yes
2	2.8 (−6.5 to 12.0)	0.32	3.2 (0.8 to 5.6)	0.029	0 (−0.7 to 0.7)	1.00	−0.1 (−1.0 to 0.7)	0.55	Yes
3	−8.1 (−102.7 to 86.5)	0.75	−8.0 (−93.7 to 77.7)	0.73	0.1 (−4.6 to 4.8)	0.93	−1.1 (−8.2 to 6.1)	0.58	No (not required)
4	5.9 (−16.6 to 28.4)	0.38	5.0 (−13.7 to 23.7)	0.37	0.6 (−1.4 to 2.7)	0.32	1.1 (−2.6 to 4.7)	0.33	Yes
5	1.8 (−25.2 to 28.7)	0.80	−5.4 (−61.2 to 50.3)	0.72	0.3 (−1.8 to 2.4)	0.59	0.2 (−2.0 to 2.5)	0.69	No
6	9.4 (−33.6 to 52.5)	0.45	18.1 (−13.4 to 49.5)	0.132	1.0 (−2.1 to 4.0)	0.30	0.7 (−0.4 to 1.9)	0.114	Yes
7	−0.2 (−2.8 to 2.3)	0.74	0.2 (−2.4 to 2.9)	0.75	0.08 (−0.3 to 0.4)	0.42	−0.02 (−0.1 to 0.06)	0.42	No
8	21.0 (−100 to 100)	0.69	12.8 (−100 to 100)	0.84	1.4 (−10 to 10)	0.73	0.6 (−10 to 10)	0.87	Yes

PIS = pain interference score; PSS = pain severity score; VAS = visual analogue scale.
* Means and 95% CIs were calculated for statin-minus-placebo differences for completed pairs. A positive mean indicates greater muscle symptoms (muscle pain for VAS myalgia score and muscle pain, weakness, or cramping for symptom-specific VAS score) while receiving statin therapy versus placebo, whereas a negative mean indicates greater muscle symptoms while receiving placebo. A positive mean for PSS or PIS indicates greater muscle pain severity or intensity, respectively, while receiving statin therapy versus placebo, whereas a negative mean indicates greater muscle pain severity or intensity, respectively, while receiving placebo. A 13-mm change in VAS score and a 1-point change in PSS or PIS were considered to be clinically significant (21–23).

Figure 3. **VAS myalgia scores for each *n*-of-1 trial, based on treatment period.**



The VAS myalgia scores for patients 1 to 8 are presented according to each treatment period (active [*solid circle, solid line*] and placebo [*solid square, dotted line*]). A full *n*-of-1 trial consisted of 6 treatment periods (3 active and 3 placebo). Treatment periods were 3 wk in duration. The VAS myalgia scores were completed at the end of each week in the treatment periods. Higher VAS myalgia scores signify greater muscle pain. Patient 6 crossed over early during treatment period 1, resulting in only 2 VAS myalgia scores for that period. Patient 7 forgot to complete 1 of 3 VASs for myalgia in treatment period 6, and patient 8 discontinued the *n*-of-1 trial after completing 5 treatment periods. VAS = visual analogue scale.

Table 4. **Combined Analysis of Differences in Pain Measures During Statin Therapy and Receipt of Placebo for all *N*-of-1 Trials**

Outcome	Mean (95% CI)*	*P* Value
VAS myalgia score	4.37 mm (−2.86 to 11.60 mm)	0.22
Symptom-specific VAS score	3.89 mm (−4.33 to 12.10 mm)	0.33
PSS	0.60 (0.06 to 1.14)	0.031
PIS	0.31 (−0.33 to 0.95)	0.32

PIS = pain interference score; PSS = pain severity score; VAS = visual analogue scale.
* Means and 95% CIs were calculated as statin-minus-placebo differences. A positive mean indicates greater muscle symptoms (muscle pain for VAS myalgia score and muscle pain, cramping, or weakness for symptom-specific VAS score) while receiving statin versus placebo, whereas a negative mean indicates greater muscle symptoms while receiving placebo. A positive mean for PSS or PIS indicates greater muscle pain severity or intensity, respectively, while receiving statin therapy versus placebo, whereas a negative mean indicates greater muscle pain severity or intensity, respectively, while receiving placebo. A 13-mm change in VAS score and a 1-point change in PSS or PIS were considered to be clinically significant (21–23).

during blinded exposures to the statin and placebo. For example, Phillips and colleagues (8) documented evidence of mitochondrial dysfunction on muscle biopsy in 4 patients who had weakness and normal CK levels but repeatedly distinguished statin therapy from placebo in a blinded setting.

Use of *n*-of-1 trials to assess statin-related myalgia is novel and capitalizes on multiple blinded rechallenges. The lack of a relationship between muscle symptoms and statin exposure in our patients' trials does not refute the clear relationship between statins and myalgia. Indeed, we are sure that expanded use of *n*-of-1 trials in patients with apparent mild statin-related myalgia would identify more patients whose symptoms are clearly caused by statins. Open-label statin rechallenge and statin switching are standard options for treating patients with myalgia. Few published data exist about the success of rechallenge with the same statin, whereas statin switching has been associated with recurrent muscle-related adverse effects in 62% to 80% of patients in a clinical setting and 73% to 100% in postmarketing surveillance (16, 31). However, these open-label experiences may carry inherent biases that lead to false conclusions that statins cause myalgia in all patients. These biases, which are best controlled in individual patients by an *n*-of-1 trial, include the effect of regression to the mean, the placebo effect (which is a negative response in the context of statin-related myalgia), and confounding by other conditions that cause muscle symptoms. Our findings show that not all patients developing myalgia during open-label statin treatment have true statin-related myopathy and that *n*-of-1 trials may be an effective way to assess statin myopathy in some patients in whom evaluation for the cause of myalgia may be difficult.

Our study has important limitations. First, our sample size was small and predominantly female and comprised highly motivated persons. Thus, our findings cannot be extended to patients who may be less motivated, less able to understand and comply with the requirements of an *n*-of-1 trial, or unwilling to consider statin use or rechallenge. Second, although the responsiveness of the VAS and BPI scores to detect minimally clinically important changes has been determined in other pain conditions, this has not yet been done in patients with statin-related myalgia. We believe it is unlikely that these properties would differ in patients with statin-related myalgia, and the BPI is currently being used in another clinical trial involving patients with statin-related myalgia (32). Third, power, or the chance of detecting a statistically significant difference in analyses of individual *n*-of-1 trials and combined results across trials, is largely measured by the number of treatment periods (14). By design, we limited this to 3 treatment pairs (3 statin and 3 placebo) per patient because other *n*-of-1 trials have done the same (33, 34). Although we may have been able to detect the statistically significant effects of statins on symptoms by completing more pairs, we judged that extending *n*-of-1 trials beyond 33 weeks would not be feasible for most patients in routine clinical practice. We also believe that the strategies we used to improve the responsiveness of the trials (choosing patients who developed myalgia while receiving several different statins, assessing other statin-associated symptoms specific to the patient, and rechallenging patients with the same statin and dose previously associated with muscle symptoms) to detect negative effects from statins helped minimize power failure. Fourth, we cannot fully exclude carryover effects in our trials. These effects can be handled by discarding earlier outcome data after a crossover or by using a sufficiently long washout period (35). We used a washout period that was of sufficient duration (3 weeks) to ensure that even statins with the longest half-life would be cleared, but we acknowledge that certain patients can take longer than 3 weeks to recover from statin-related myalgia. As a more general observation on the statistical limitations of our *n*-of-1 trials, we suspect that their value in reaching an objective treatment decision in a single patient compared with the standard approach of open-label statin rechallenge is more in the design (prospective determination of the patient's responses, use of placebo controls, random allocation, and multiple exposures) than in the statistical analysis.

The treatment of patients with statin-related myalgia has primarily focused on continuing to administer a statin, if possible, by open-label methods using statin rechallenge, statin switching, or alternate dosing schedules (7). However, selected patients develop recurrent myalgia despite use of different statins, and these cases are often confounded by factors (whether medical or environmental) that also contribute to myalgia or generalized pain, such as fibromyalgia, arthritis, or a job with varying levels of physical exertion. Given the waxing and waning nature of such confounders, patients and physicians may have difficulty determining how much of current pain symptoms are due to a statin versus an exacerbation of a preexisting pain-

generating factor. For such patients, in whom open-label statin rechallenge or statin switching has been attempted several times but the results may be confounded by such factors, *n*-of-1 trials may provide a useful method for ascertaining the unbiased occurrence of myalgia in relation to statin use.

In conclusion, our results support proof of the concept that *n*-of-1 trials can improve the assessment of statin-related myalgia in selected patients. The potential for expanded use of *n*-of-1 trials for statin-related myalgia, including use in routine clinical practice, is not clear. Although such trials are more complex than standard practice, some centers have established centralized *n*-of-1 trial services that reduce the burden on individual physicians (36). Given the importance of statin-related myalgia, larger studies of *n*-of-1 trials for this condition that include longer follow-up and comparison with concurrent control groups should be considered.

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