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Original Article

Statin intolerance in a referral lipid clinic

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BACKGROUND: Statins effectively prevent atherosclerotic cardiovascular disease, but rates of statin discontinuation after adverse events are high.

OBJECTIVE: Describe the range and relative frequencies of adverse events potentially attributable to statins in lipid referral practice and assess statin rechallenge outcomes.

METHODS: Retrospective cohort study of 642 patients with statin-associated adverse events evaluated in a referral lipid clinic between January 1, 2004 and January 27, 2011.

RESULTS: Patients experiencing adverse events by organ system included 92% with musculoskeletal, 8% central nervous system, 10% liver, 8% gastrointestinal, 5% peripheral nervous system, 5% skin, and 3% other events. Overlap of organ system involvement occurred in 22.5%. At least 1 follow-up visit was made by 557 patients, among whom overall median follow-up was 25 months. Among patients treated with a statin in the clinic, 71% remained on a statin at the last follow-up visit. Patients with hepatic transaminase increases by history were numerically more likely than the overall group to reassume or remain on statin treatment, whereas those reporting central nervous system or gastrointestinal symptoms trended lower for statin maintenance. Among patients who experienced an adverse event after statin rechallenge, the majority (64%) were being treated with intermittent, non-daily dosing at the time of the adverse event.

CONCLUSION: Although musculoskeletal symptoms are reported by 90% of patients with statin intolerance, symptoms involving other organ systems may be more frequent than previously supposed. Understanding the range of symptoms, time course, and impact on daily activities informs counseling in patient-centered practice, but assessment of causation by statins remains challenging.
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Treatment with a statin to lower low-density lipoprotein cholesterol is a cornerstone for prevention of atherosclerotic cardiovascular disease (ASCVD) in people with high risk, based on randomized clinical trials and emphasized in recent guidelines and recommendations.[1,2] However, the

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fraction of people who discontinue statin treatment is high.[3-5] In 2 academic clinical practice groups, 16% of patients with an initial prescription discontinued statin treatment, evidenced by no subsequent prescription over 1 year.[5] Among respondents for a consumer panel survey of those who ever used statins, 12% were former and 88% current statin users.[3] Among the current statin users, 25% reported muscle-related side effects that could potentially limit statin dosing. Thus, intolerance to statin therapy limits adherence to lipid-lowering recommendations for many individuals with consequent failure to prevent ASCVD.[1,2]

A major discrepancy exists between high rates of statin intolerance in clinical practice and the lack of support from randomized clinical trials for biologic causation of musculoskeletal and other adverse effects associated with statins.[3,6-8] In a systematic review of 26 trials including 113,695 participants, Ganga et al. found that muscle aches or pains were reported by 12.7% of those assigned to statins and 12.4% of placebo subjects, suggesting a difference of only 0.3%.[6] Misattribution of symptoms in practice undoubtedly occurs, but the possibility that clinical trials have not addressed the problem adequately must also be considered. Subjects with predisposing comorbidities or statin intolerance history may not qualify for or may avoid clinical trials, and others may terminate during run-in periods. Assessment of graded symptomatic intolerance may require evaluative methods different from those used primarily for efficacy and safety.[9,10] Few placebo-controlled randomized trials have evaluated statin-associated adverse events as a primary endpoint.[11,12] No validated clinical scale for statin intolerance has been achieved.[7]

Faced with the disparate evidence, a consensus panel of the National Lipid Association identified at least 3 perspectives that dictate different definitions of statin intolerance in different settings: a patient-centered perspective encountered in clinical practice, a population perspective based on rigorous scientific evidence, and a regulatory or counseling or reimbursement perspective conceived as mediating between the former two.[9,10]

Reconciling these perspectives and addressing patient concerns adequately requires a combination of observational studies and randomized clinical trials. Prior observational studies have focused on muscle problems, on academic health system practice, on intermittent vs daily statin dosing, and on symptoms reported by respondents to advertising for statin-associated problems.[4,5,8,13-15]

Here, we present a retrospective evaluation of 642 consecutive patients with statin intolerance seen in a single academic referral lipid clinic over a 4-year period. We give particular attention to defining the range of symptoms described, variability of presentation, involvement of organ systems other than muscle, and the results of statin therapy challenges while in the lipid clinic. The perspective of this analysis is patient-centered, implying that the data attempt to reflect without bias the patients' own descriptions of symptomatic adverse events.

A single attending lipid specialist (JRG) personally saw and evaluated every patient. Although the patient can be advised that not all intolerance is caused biologically by the statin, a patient-centered perspective requires that the medical provider defer to patient preference and judgment, and proceed toward the best mutually agreeable treatment course. Generally the safety of statins and the LDL-reducing effectiveness of lower statin doses that avoid nontarget effects were emphasized in our clinic practice. In the great majority of cases, a suggestion was made to reinstitute the same or a different statin at a lower effective dose and to uptitrate slowly until the patient perceived interference with activities of daily living such as sleep, work, exercise, and enjoyment of leisure. This practice is similar to that described in a recent review.[16]

We undertake this patient-centered analysis of the breadth of statin-associated adverse effects with goals of improving counseling and facilitating provider-patient agreement in the practice setting, as well as informing the design of future randomized, double-blind trials of statin intolerance.

Methods

Study design

This is a retrospective cohort study of all consecutive adult patients (≥18 years) treated in the Duke University Medical Center Lipid Clinic between January 1, 2007 and January 27, 2011 with a putative diagnosis of a statin-associated adverse event recorded in the medical record. Lipid assessment and therapy were directly managed or supervised by one lipid specialist (JRG).

Demographic data, medical history, adverse events attributed to lipid-lowering therapies, prior and current medications, physical examination, and laboratory data were recorded in the medical record at each clinic visit as part of routine care. Statin-associated adverse events noted at the baseline clinic visit were defined as patient or referring provider reports of prior potential reactions to statin therapy. While treated in the lipid clinic, statin-associated adverse events were defined as adverse events temporally associated with and suspected by patient or provider as attributable to statin use. Adverse events were recorded if the patient developed a new symptom or had worsening of a pre-existing symptom during statin use. In addition, symptoms or laboratory abnormalities that led to a reduction in the statin total daily dose or discontinuation of statin were also recorded as an adverse event.

Study cohort

Adult patients with a putative diagnosis of statin-associated adverse events with at least one visit to the lipid clinic during the study period were included. The initial