In a wide range of patients with and without heart disease, 1-3 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce cardiovascular morbidity and mortality. Ongoing research is investigating the possible role of statins in the treatment of dementia, hypertension, diabetes mellitus, and arthritis. Because of the cardiovascular benefits and improved survival among patients receiving statins, these medications are now the most prescribed class of drugs in the United States.10 Statin use is expected to increase with the advancing age of society and as additional benefits of statins are clarified.11

These 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors may cause myotoxic effects, with muscle pain occurring in 2% to 11% of patients, and clinically significant myopathy, defined as a creatine kinase (CK) level more than 10 times the reference value, with associated muscle symptoms occurring in approximately 0.5% of patients.12-15 The Heart Protection Study16 identified no significant difference in the incidence rate of myotoxic effects between individuals receiving a statin vs placebo. However, individuals with coexisting diseases or taking medications that predispose to myotoxic effects were excluded from this study.

Known risk factors for the development of statin-associated myopathy include coexisting diseases associated with rhabdomyolysis (renal insufficiency, hepatic dysfunction, and hypothyroidism) and the use of concomitant medications that interfere with statin metabolism or independently cause myositis (gemfibrozil, cyclosporine, macrolide antibiotics, niacin, azole antifungals, protease inhibitors, and calcium channel blockers).17 The natural course of myopathy in clinical practice is unknown, with only case reports or small case series describing short-term outcomes.16-31 Such published reports may select patients with more dramatic or unique presentations, potentially leading to a selection or publication bias and, therefore, an inaccurate characterization of the typical presentation and outcome of statin-associated myopathy.
We hypothesized that statin-associated myopathy is self-limited, with a benign clinical outcome, based on similar outcomes among patients in our own practices. We initiated a retrospective study to investigate the time course, severity, and clinical outcomes of patients experiencing statin-associated myopathy at a single medical center.

**METHODS**

**CASE ASCERTAINMENT**

We performed a retrospective study at the University of Wisconsin Hospital and Clinics, a tertiary care academic medical center in Madison. The human subjects committee of the University of Wisconsin Medical School approved the study. Informed consent from study participants was waived because the study was of minimal risk and could not practically occur without a waiver.

To identify potential cases of myotoxic effects, the University of Wisconsin Hospital and Clinics Medical Informatics Department provided a list of patients with International Classification of Diseases, Ninth Revision codes for myositis (code 729.1); myopathy (code 359.9); myopathy due to drugs (code 359.4); inflammatory myopathy (code 359.8); progressive myopathy (code 359.8); toxic myopathy (359.4); other disorders of muscle, ligament, and fascia (codes 728.8 and 728.89); muscle weakness (code 728.9); unspecified myalgia and myositis (code 729.1); and adverse drug reaction to a cholesterol-lowering agent (codes E942.2, E980.4, and E972.2). All inpatients and outpatients seen at the University of Wisconsin Hospital and Clinics between January 1, 1990, and October 1, 2003, were included in this initial search (N=437). On review of 437 medical records, we excluded patients with an underlying primary or secondary myopathy or an associated myopathy at a single medical center.
Serum CK levels were measured in 37 patients (82%), with a mean value of 10 160 (28 879) U/L and a median value of 328 U/L (range, 36-140 190 U/L). The serum CK levels were within the reference range for 13 patients (35%). We found no statistical relationship between peak serum CK level and the presence of weakness and the duration or severity of muscle pain. Sixteen patients (36%) underwent thyrotrpin testing within 2 months of the episode of myopathy; no individual had overt hypothyroidism.

Six of 8 patients with clinically significant myopathy were admitted to the hospital for the management of rhabdomyolysis. The serum CK levels of these patients were significantly higher than those of individuals treated as outpatients (Table 2). Three hospitalized patients experienced renal dysfunction. This first patient (peak CK level, 35 140 U/L) developed acute tubular necrosis (peak serum creatinine concentration, 6.2 mg/dL [548 µmol/L]) and during the following 3 months experienced recovery of normal renal function. The second patient (peak serum CK level, 11 928 U/L) developed mild renal insufficiency (peak serum creatinine concentration, 1.6 mg/dL [141 µmol/L]) but had normalization of renal function by the time of hospital discharge. The third patient (peak serum CK concentration, 7000 U/L) had preexisting renal artery stenosis and required dialysis during her hospitalization; her admission creatinine concentration of 2.1 mg/dL (186 µmol/L) increased to 4.6 mg/dL (407 µmol/L) by discharge. Subsequent outpatient renal stenting did not delay progression to end-stage renal disease, and she now receives lifelong dialysis.

Patients with clinically significant myopathy were older than those without this degree of myositis (66.1 [9.2] vs 57.4 [9.1] years; P= .02) but were similar in other patient characteristics (data not shown). In hospitalized patients, the duration of statin therapy before the onset of muscle pain was significantly shorter than that in individuals treated as outpatients (1.3 [0.8] vs 7.1 [10.0] months; P= .048) (Table 2).

Like other investigators, we found that the use of combination therapy was more common in patients hospitalized for rhabdomyolysis (P= .03) (Table 2). Specifically, 3 patients developed rhabdomyolysis within 1 month of simultaneously beginning therapy with 2 lipid-lowering drugs (simvastatin and niacin added to long-term verapamil hydrochloride, simvastatin and gemfibrozil added to asprin hydrochloride, simvastatin and niacin added to long-term verapamil hydrochloride).
long-term verapamil, and cerivastatin sodium plus gemfibrozil). The fourth individual tolerated gemfibrozil monotherapy for 2 months but experienced rhabdomyolysis within 1 month of adding cerivastatin. A fifth individual, who was already taking diltiazem hydrochloride, experienced rhabdomyolysis within 2½ weeks of beginning treatment with a study statin. The sixth person was taking felodipine and within 2 months of starting cerivastatin therapy sustained rhabdomyolysis.

To exclude other causes of myopathy, 5 patients underwent muscle biopsy or electromyography with assessment of nerve conduction velocity. Findings from the latter were normal in all the patients (n = 4). Muscle biopsy histologic findings were normal in 2 patients, demonstrated muscle necrosis without inflammation in a third, and revealed nonspecific myopathy in a fourth. We did not detect differing clinical characteristics between patients undergoing muscle biopsy and those managed without such additional testing (Table 3). No patient developed permanent liver dysfunction, defined by elevated total bilirubin or alkaline phosphatase levels in addition to elevated transaminase levels.

LONGITUDINAL DATA

Of 44 patients for whom data were available, the mean duration of statin therapy before symptom onset was 6.3 (9.8) months (range, 0.25-48.0 months) (Table 4). More specifically, approximately one third of the patients (n = 17) noted muscle pain within 1 month and another one third (n = 16) within 6 months of beginning statin therapy.

Thirty medications known to increase the risk of statin-associated myopathy were prescribed to 23 patients (52%). Concomitant medications associated with an episode of statin-associated myopathy included calcium channel blockers (n = 9), niacin (n = 5), gemfibrozil (n = 4), macrolide antibiotics (n = 2), nefazodone hydrochloride (n = 2), cyclosporine (n = 2), and miscellaneous medications (n = 1 each for amiodarone, cholestyramine, fenofibrate, fluoxetine hydrochloride, sertraline hydrochloride, and trimethoprim-sulfamethoxazole). Among patients taking cyclosporine, one received simvastatin, 20 mg daily, with subsequent myopathy and the other reported muscle pain while taking pravastatin sodium, 10 mg daily, and later tolerated this statin without recurrent symptoms.

In 44 patients, medical records indicated recovery from statin-associated myopathy a median of 2.3 (3.0) months after the cessation of statin therapy (range, 0.25-14.0 months) (Table 4). Specifically, 57% of the patients (n = 25) reported resolution of muscle symptoms by 1 month, another 34% (n = 15) by 6 months, and 7% (n = 3) by 14 months after stopping statin use. The single patient with ongoing muscle pain chose to continue statin therapy because of the high risk of cardiovascular disease. One individual reported “several months” of pain before full recovery.

Thirty-seven patients received other statins after an episode of statin-associated myopathy, with medical records providing adequate documentation of a response to that statin. Of these patients, 57% (n = 21) reported recurrent muscle pain with the use of other statins. Conversely, 43% (n = 16) tolerated a different statin (n = 12) or the same statin (n = 4) after an episode of statin-associated myopathy. Of 4 patients tolerating the same statin, 1 noted muscle pain with the statin and also a macrolide antibiotic that resolved with discontinuation of the treatment with macrolide despite continued use of amiodarone. Another patient tolerated a lower dose of simvastatin without pain, whereas 2 patients tolerated the statin at the same dose (n = 1) or an unknown dose (n = 1), in the latter case despite continuation of cyclosporine and trimethoprim-sulfamethoxazole treatment.

Of 6 patients hospitalized for rhabdomyolysis, 4 received other statins after recovery from myositis. The first
patient developed rhabdomyolysis with use of simvastatin and niacin and later reported flank pain with atorvastatin calcium; verapamil was prescribed throughout this period. The second patient experienced rhabdomyolysis while taking cerivastatin and gemfibrozil but later did well while taking atorvastatin. The third patient with rhabdomyolysis while receiving cerivastatin and gemfibrozil also reported muscle pain while taking simvastatin. The final patient recovered from rhabdomyolysis while taking simvastatin, gemfibrozil, and verapamil and then tolerated pravastatin despite concurrent use of verapamil and fenofibrate. Thus, although the data are limited, these findings suggest that some patients with rhabdomyolysis from one statin can tolerate other statins without recurrent symptoms.

We sought but did not find predictors of intolerance to more than 1 statin. Specifically, patient age, sex, duration of statin therapy before the onset of myopathy, duration of muscle pain, and peak serum CK level were no different between individuals with and without tolerance to other statins (Table 5). Likewise, disparate use of concomitant medications known to increase the risk of statin-associated myopathy was not observed between the tolerant and intolerant groups. Patients with intolerance to other statins had a higher creatinine clearance (P = .006), but this variable was available only for 32 individuals.

COMMENT

Because statin use is widespread, most primary care providers will encounter patients who experience an episode of statin-induced myopathy. Understanding the natural course of statin-associated myopathy will facilitate better informed consent of patients initiating such therapy and will allow caregivers to provide more complete information to their patients regarding the prognosis of the condition.

This study of statin-associated myopathy provides a spectrum of observations ranging from mild muscle pain to acute rhabdomyolysis. We describe important clinical details of statin-associated myopathy, including location of muscle pain, frequency of muscle weakness, time course of the illness, and ability to tolerate other statins after an episode of statin-associated myopathy. Like other researchers, we found that rhabdomyolysis is often associated with the use of coexisting medications known to increase its risk. In addition, patients with clinically significant myopathy were older than those without this degree of myositis.

Every patient who discontinued statin therapy experienced rapid resolution of muscle pain, typically within a month after cessation of therapy. Renal dysfunction was usually temporary but occurred in half of the patients who required hospitalization for rhabdomyolysis. Finally, although data are limited, our findings suggest that some patients with statin-associated rhabdomyolysis may tolerate other statins without recurrent symptoms.

The most important limitation of this study is its retrospective, observational nature. We relied on health care providers to record clinical details and to order objective tests of muscle function, such as the serum CK measurement. This study may involve selection or referral bias because patients receiving care in a tertiary center may be different from those treated in private practice. In addition, we used clinical outcomes, and most patients did not undergo objective muscle tests, such as electromyography or muscle biopsy, during or after an episode of statin-associated myopathy. The small sample size of this study is an important limitation; our study had limited power to detect individual patient characteristics that may predict adverse outcomes from statin-associated myopathy. Finally, the data from this study cannot be used to assess the incidence of myopathy with each statin.

In this study, patients with statin-associated myopathy experienced full resolution of muscle pain on the cessation of statin therapy. Although no deaths occurred, 13% of the patients required hospitalization for rhabdomyolysis, and half of these individuals experienced transient or permanent renal dysfunction. Recurrent muscle pain was common on statin rechallenge, but predictors of intolerance to multiple statins were not identified in this small study.

Accepted for Publication: July 12, 2005.

Correspondence: Karen E. Hansen, MD, Rheumatology Section, University of Wisconsin Medical School, Mailbox 3244, H6/363 Clinical Science Center, 600 Highland Ave, Madison, WI 53792 (keh@medicine.wisc.edu).

Financial Disclosure: Dr Ferguson is on the speaker's bureaus and has received grant support from Pfizer and KOS Pharmaceuticals. Dr Stein is on the speaker's bureaus of KOS Pharmaceutical, Merck, Pfizer, and Schering-Plough and has received grant support from AstraZeneca and Bristol-Myers Squibb.

Funding/Sponsor: This study was supported by grants 1K23 AR050995 and 1K12RR017614 (Dr Hansen) and

Table 5. Clinical Variables and Intolerance to More Than 1 Statin

<table>
<thead>
<tr>
<th>Patient Variable</th>
<th>Tolerant (n = 16)</th>
<th>Intolerant (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>59.8 (12)</td>
<td>55.8 (7)</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>5 (31)</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Duration of statin therapy before myopathy, mean (SD), mo</td>
<td>8.4 (11)</td>
<td>5.4 (10)*</td>
</tr>
<tr>
<td>Duration of myalgia after stopping statin therapy, mean (SD), mo</td>
<td>2.3 (3.4)</td>
<td>1.6 (1.4)*</td>
</tr>
<tr>
<td>Peak serum creatine kinase, mean (SD), U/L</td>
<td>11 271 (28 081)†</td>
<td>11 039 (34 779)‡</td>
</tr>
<tr>
<td>Combination therapy, No. (%)§</td>
<td>10 (63)</td>
<td>8 (40)*</td>
</tr>
<tr>
<td>Creatinine clearance, mean (SD), mL/min</td>
<td>48 (23)†</td>
<td>70 (12)†</td>
</tr>
</tbody>
</table>

§Combination therapy refers to use of a concomitant medication known to increase the risk of statin-associated myopathy.
¶Conversion factor: To convert creatinine clearance to milliliters per second, multiply by 0.0167.
*Data were unavailable for 1 patient (n = 20).
†Data were unavailable for 4 patients (n = 12).
‡Data were unavailable for 4 patients (n = 17).
§Statistically significant difference between groups (P < .05).
grant K23 RR16176-01 (Dr Stein) from the National Institutes of Health, Bethesda, Md.

Acknowledgment: We thank Don Wiebe, PhD, for information regarding CK assays.

REFERENCES


