Which statin is associated with the lowest risk of myalgia?
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At this time, there are 7 agents in the 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor or "statin" drug class.[1] The drugs are atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. All drugs in this class have been associated with myopathy, defined as muscle disease, which typically manifests as myalgia (muscle pain, tenderness, or weakness) with or without an increase in creatine phosphokinase (CPK). The *Pharmacist's Letter* reports that up to 30% of patients taking statin drugs develop muscle pain or weakness.[2,3] The mechanism for this reaction has not been fully elucidated; it has been suggested that statins may inhibit the production of substances involved in cell respiration (e.g., dolichols, isoprenylated proteins, and coenzyme Q10) and induce apoptosis.

Several risk factors for statin-induced myopathy have been described in the literature. Per *Facts and Comparisons*, the risk of myopathy and its more severe form, rhabdomyolysis, is dose-related and may increase with concurrent administration of drugs inhibiting statin metabolism.[1] Additionally, the risk of myopathy may be increased with lipophilic statins, due to higher distribution in the musculature (e.g., atorvastatin, lovastatin, simvastatin), compared to hydrophilic statins (e.g., pravastatin, rosuvastatin, fluvastatin).[1,4] Notably, these effects have been observed in animal models and have not been evaluated in humans.[5] Risk of myopathy has also been attributed to drugs with longer elimination half-lives (e.g., rosuvastatin, atorvastatin).[1,4,] Other risk factors include advanced age (>75 to 80 years), small body frame (low body mass index), changes in albumin and α-1 glycoprotein levels, multisystem disease (e.g., chronic renal insufficiency), substance abuse, and use of interacting drugs or food (leading to increased statin levels).[4-8]

Myalgia has been reported at varying incidences among the statins. *Facts and Comparisons* reports incidences as low as 0.6% to 1.4% with pravastatin and up to 12.7% with rosuvastatin (see Table 1).[1] These data were obtained from placebo-controlled trials;[9-15] to date, no published studies have been identified that directly compare occurrence of muscle pain among all of the statins.[5]

Table 1. Incidence of myalgia among statin drugs.[1,9-15]

Drug	Incidence of myalgia
Atorvastatin	≤5.6%
Fluvastatin	3.8% to 5%
Lovastatin	1.8% to 3%
Pitavastatin	3.1%
Pravastatin	0.6% to 1.4%
Rosuvastatin	2.8% to 12.7%
Simvastatin	3.7%

McClure et al conducted a meta-analysis of randomized controlled trials involving statins to determine the association of clinically relevant adverse events.[16] The investigators included double-blind, placebo-controlled trials involving statin monotherapy, published from 1982 through June 2006 and evaluated statin discontinuation rates and muscle-related symptoms. A total of 119 studies were included, involving >86,000 patients with a mean age of 59 years. The study durations ranged from 1 week to 5 years. Of the currently available statins, pitavastatin was not included; studies involving cerivastatin, a drug withdrawn

from the market in 2001, were included. (Notably, cerivastatin was withdrawn due to reports of fatal rhabdomyolysis).

In total, the statins were associated with a non-significant increase in the risk of myalgia (odds ratio [OR] 1.74, 95% confidence interval [CI]: 0.51 to 5.91).[16] Excluding cerivastatin, the risk was still elevated but to a much lower extent (OR 1.09, 95% CI: 0.97 to 1.23). The investigators did not report the incidence of myalgia associated with each statin; however, they did assert that myositis was observed in 10 trials (involving simvastatin, lovastatin, atorvastatin, pravastatin, and cerivastatin) and rhabdomyolysis was observed in 4 trials (involving simvastatin, lovastatin, and atorvastatin). No conclusions were drawn as to the safety of the individual statins.

In another meta-analysis, Silva et al sought to determine the comparative frequencies of adverse events among statins.[17] The investigators included randomized controlled trials involving atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, and lovastatin. A total of 18 trials were identified, involving 71,108 patients. Overall, adverse events were reported most frequently with atorvastatin and least frequently with fluvastatin. Myalgia was observed to be lower in patients receiving fluvastatin vs. atorvastatin (OR 0.276, 95% CI: 0.175 to 0.437) and lower in patients receiving pravastatin vs. atorvastatin (OR 0.428, 95% CI: 0.360 to 0.510). Myalgia also occurred less frequently in patients receiving pravastatin vs. simvastatin (OR 0.532, 95% CI: 0.437 to 0.648). A lower but non-statistically significant risk for myalgia was determined for fluvastatin vs. pravastatin (OR 0.645, 95% CI: 0.409 to 1.017), while an increased but non-statistically significant risk for myalgia was determined for fluvastatin vs. simvastatin (OR 1.212, 95% CI: 0.759 to 1.934). Despite this, in consideration of myalgia as well as other adverse events, including rhabdomyolysis, CPK changes, and liver function test changes, the authors concluded that statins ordered from highest to lowest risk were atorvastatin > pravastatin = simvastatin = lovastatin > fluvastatin.

Bruckert et al evaluated the occurrence of muscular symptoms in patients receiving high-dose statin therapy (PRIMO study).[18] This was an observational study in which patients with hyperlipidemia were included if using fluvastatin 80 mg/d, atorvastatin 40 to 80 mg/d, pravastatin 40 mg/d or simvastatin 40 to 80 mg/d for at least 3 months prior to enrollment. A total of 7,924 patients were assessed, 882 of whom developed muscular symptoms. Occurrence of muscular symptoms was reported in 18.2% of simvastatin users, 14.9% of atorvastatin users, 10.9% of pravastatin users, and 5.1% of fluvastatin users. Simvastatin was associated with the highest risk of muscle pain (OR 1.78, 95% CI 1.39 to 2.29, vs. pravastatin), followed by atorvastatin (OR 1.28, 95% CI: 1.02 to 1.60, vs. pravastatin). Fluvastatin was associated with the lowest risk of muscular symptoms (OR 0.33, 95% CI: 0.26 to 0.42).

Most recently, Naci et al conducted a meta-analysis evaluating the comparative tolerability of statins.[19] The investigators included randomized controlled trials of all 7 statins with >50 subjects and duration >4 weeks. Relative harms were quantified using pairwise and network comparisons. A total of 55 placebo-controlled trials and 80 active-controlled trials were included. Overall, there were no significant differences between statins and their comparators in myalgia (OR 1.07, 95% CI 0.89 to 1.29, I^2=22.1%). Pairwise analyses of trials comparing simvastatin to atorvastatin indicated lower odds of myalgia with simvastatin (OR 0.56, 95% CI 0.42 to 0.75, I^2=0.0%). However, network comparisons revealed no significant differences in myalgia among the individual statins. Despite this, Naci et al noted significant differences in other aspects of tolerability favoring pravastatin and simvastatin, including lower

incidences of transaminase and CPK elevations and fewer discontinuations due to adverse events. Though not statistically significant, occurrence of myalgia was also lower among patients taking pravastatin or simvastatin.

Based on the available literature, there is no clear consensus on which statin is associated with the lowest risk of myalgia. Both fluvastatin and pravastatin are hydrophilic and may have a lower propensity for drug interactions compared to the other statin drugs. Also, fluvastatin has low bioavailability and is highly protein-bound. Rosuvastatin, though not included in the PRIMO study, is also hydrophilic with a low propensity for drug interactions, but its elimination half-life is long.

Importantly, when considering a statin, other factors such as potency (i.e., effect on low-density lipoprotein [LDL] cholesterol levels) should be considered. While pravastatin and fluvastatin may be associated with the lowest incidence of myalgia, the LDL-lowering effect is low compared to other statins.[20] The highest dose (80 mg/d) of pravastatin and fluvastatin have been associated with LDL lowering of 37% and 35%, respectively. For comparison, rosuvastatin 40 mg/d has been associated with LDL reductions of 55% to 63% and atorvastatin 80 mg/d has been associated with LDL reductions of 55% to 60%. The relative potency should be considered in conjunction with the relative risk for myopathy and other adverse events, as well as patient-specific factors in the determination of appropriate therapy.

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