Savvy Statin Shopping

Let's go shopping. This edition of Staying Well focuses on how to be a savvy shopper in choosing a statin for your patients, a timely issue in light of the US Food and Drug Administration's (FDA's) new simvastatin warnings. Seasoned shoppers always check the sale racks first, but don't buy something -- even if on sale -- if the "size and style" aren't right. Apply this analogy to picking a statin. Although the first thing to look for is price, it should not be the only deciding factor. Simvastatin is certainly one of the cheapest statins, but is it the best choice for your patients?

My Personal Disclaimer

I admit that I have been a little lazy. For the last several years, when my patients needed statins I always started with simvastatin. It was generic. It was on all the pharmacy plans, so the price point for patients was right. Prescribing was hassle free: no cumbersome forms to fill out and explain. However, the recent FDA warnings about the dangers of high-dose simvastatin and additional warnings about dosing and drug interactions have led me to rethink this strategy and take a closer look at the different statins available. It is now time to find out the facts and make necessary changes in prescribing patterns. Maybe it's time for a new "style" of treatment. Here is some information to help you decide.

Statin Characteristics

This statin dose equivalency guide gives equivalent doses of available statins along with generic and brand names and selected characteristics (Table 1).[1-5]

Table 1. Statin Dose Equivalency Guide

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose Equivalent</th>
<th>Pharmacotherapeutic Factor</th>
<th>Metabolism</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin (Crestor®)</td>
<td>2.5 mg</td>
<td>Hydrophilic</td>
<td>CYP2C9</td>
<td>Active (minor) metabolite</td>
</tr>
<tr>
<td>Atorvastatin (Lipitor®)</td>
<td>5 mg</td>
<td>Lipophilic</td>
<td>P450 3A4 (CYP3A4)</td>
<td>Active metabolite</td>
</tr>
<tr>
<td>Simvastatin (Zocor®)³</td>
<td>10 mg</td>
<td>Lipophilic</td>
<td>P450 3A4 (CYP3A4)</td>
<td>Active metabolite</td>
</tr>
<tr>
<td>Lovastatin (Altoprev®, Mevacor®)</td>
<td>20 mg</td>
<td>Lipophilic</td>
<td>P450 3A4 (CYP3A4)</td>
<td>Active metabolite</td>
</tr>
<tr>
<td>Pravastatin (Pravachol®)</td>
<td>20 mg</td>
<td>Hydrophilic</td>
<td>Renal metabolism</td>
<td>No active metabolites</td>
</tr>
</tbody>
</table>
Fluvastatin
(Lescol®, Lescol® XL)  
| 40 mg | Lipophilic | CYP2C9 | No active metabolites |
---|---|---|---|
Pitavastatin (Livalo®)  
| 1 mg | Lipophilic | Little metabolism by CYP3A4 | No active metabolites |

\(^a\)Also in combination medications: ezetimibe/simvastatin (Vytorin®) and niacin extended release/simvastatin (Simcor®)

Table 2 is from the FDA Drug Safety Communication and gives relative low-density lipoprotein (LDL) efficacy for the different statins. Note that pitavastatin (Livalo®) is a newer statin and was FDA approved in 2009.

**Table 2. Relative LDL-Lowering Efficacy of Statin and Statin-Based Therapies**

<table>
<thead>
<tr>
<th>Atorva</th>
<th>Fluva</th>
<th>Pitava</th>
<th>Lova</th>
<th>Prava</th>
<th>Rosuva</th>
<th>Vytorin(^a)</th>
<th>Simva</th>
<th>%↓ LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>--</td>
<td>40 mg</td>
<td>1 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>--</td>
<td>--</td>
<td>10 mg</td>
<td>30%</td>
</tr>
<tr>
<td>10 mg</td>
<td>80 mg</td>
<td>2 mg</td>
<td>40/80 mg</td>
<td>40 mg</td>
<td>--</td>
<td>--</td>
<td>20 mg</td>
<td>38%</td>
</tr>
<tr>
<td>20 mg</td>
<td>--</td>
<td>4 mg</td>
<td>80 mg</td>
<td>80 mg</td>
<td>5 mg</td>
<td>10/10 mg</td>
<td>40 mg</td>
<td>41%</td>
</tr>
<tr>
<td>40 mg</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>10 mg</td>
<td>10/20 mg</td>
<td>80 mg</td>
<td>47%</td>
</tr>
<tr>
<td>80 mg</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>20 mg</td>
<td>10/40 mg</td>
<td>--</td>
<td>55%</td>
</tr>
<tr>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>40 mg</td>
<td>10/80 mg</td>
<td>--</td>
<td>63%</td>
</tr>
</tbody>
</table>

\(^a\)No incremental benefit of Vytorin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.


**Association of Pharmacologic Factors With Adverse Effects**

Statins that are hydrophilic (pravastatin and rosuvastatin) are less likely to cross skeletal muscle membranes and are less likely to cause adverse effects.[3]

Statins that don't have active metabolites (fluvastatin, pravastatin, and pitavastatin) are less likely to cause adverse effects. Rosuvastatin has only a minor active metabolite.[3,5]

Drug metabolism pathway plays a role in drug-drug interactions and subsequent safety. This is especially important for patients on multiple medications:

- For statins metabolized by P450 3A4 (CYP3A4) (simvastatin, lovastatin, atorvastatin), concomitant administration of medications that inhibit the CYP3A4 pathways (protease inhibitors, cyclosporine, amiodarone, fibrates) is problematic. The result is increased statin levels and increased risk for muscle tissue injury.
- On the other hand, fluvastatin and rosuvastatin (metabolized by CYP2C9) and pravastatin (metabolized by the kidneys) are considered to be safer statin choices for patients on multiple medications.[3]

**The Simvastatin Saga: Review of the FDA Drug Safety Warnings**

On June 8, 2011, with the release of the FDA warnings, the simvastatin sales bonanza was doomed. Here are the highlights.
**High-Dose Simvastatin: Prescribe 80 mg No More**

The FDA said no "new" prescriptions for high-dose simvastatin (80 mg). The FDA says that the 80 mg is satisfactory if patients have been on it for a year with no evidence of myopathy. However, to me, with what we know now, continuing to prescribe the 80-mg dose even in patients who had been stable is like hiring a known child molester as a babysitter.[4,6]

**Restrictions on Intermediate- and Low-Dose Simvastatin: Is 40 mg the New 80 mg?**

Not necessarily. There are more restrictions:

- New: No more than 20 mg for patients taking amlodipine (Norvasc®) and ranolazine (Ranexa®); and
- No more than 10 mg for patients on amiodarone, verapamil, and diltiazem.[4,6]

**Restrictions for Simvastatin at Any Dose**

The FDA has mandated drug labeling changes warning that simvastatin is contraindicated in patients on gemfibrozil; antifungal medications including itraconazole (Sporanox®), ketoconazole (Nizoral®), posaconazole (Noxafil®); antibiotics such as erythromycin, clarithromycin, telithromycin (Ketek®); and HIV protease inhibitors, nefazodone, cyclosporine, and danazol.[4,6]

This information is not totally new. In 2004, when the A to Z trial was published in JAMA, the Cleveland Clinic's Dr. Steven Nissen's editorial expressed his concerns about increased rates of myopathy in patients on simvastatin.[7] The most recent study to cast dispersions on simvastatin was SEARCH published in The Lancet in 2010, which linked simvastatin 80-mg doses of simvastatin to increased risk for myopathy.[4,8] Why the FDA didn't act sooner is not clear, but the word is out now. Simvastatin concerns are in the public domain. Patients know about them, and they depend on us to clean up their medication regimens.

**Mechanisms of Statin-Related Muscle Injury**

As many as 10% of patients on statin therapy suffer muscle-related adverse effects. There are several proposed statin-induced mechanisms:

- Decreases in cholesterol content of skeletal muscle membranes making them unstable and thus more prone to injury;
- Depletion of coenzyme Q10 with subsequent deleterious effects on mitochondrial function; and
- Reduced bioavailability of isoprenoids (farnesyl pyrophosphate and geranyl pyrophosphate), which can lead to cell death in vitro.[9]

Genetics play a role. A 2010 FDA drug safety communication emphasized that patients of Chinese descent are more likely to suffer simvastatin-induced muscle side effects.[10] A recent study showed carriers of the SLCO1B1 gene polymorphism had increased risk for muscle-related statin adverse effects. The greatest risk was seen in patients on simvastatin, whereas the risk for patients on pravastatin was almost negligible.[11]

Statin-related muscle adverse effects are dose related: The higher the dose, the greater the risk for muscle-related side effects. The type of statin used also matters. In the PRIMO (Paricalcitol Capsules Benefits in Renal Failure Induced Cardiac Morbidity in Subjects With Chronic Kidney Disease) study, the lowest rate of muscle symptoms was seen in patients on fluvastatin.[9]

Who is at greatest risk? Women, older patients, patients on high statin doses, people with a family history of statin intolerance, and patients on multiple medications are among those at greatest risk of suffering statin-related muscle side effects.[9]

**Muscle Aches: Ordinary vs Problematic**
Muscle soreness due to physical activity usually peaks 2 days after strenuous activity and lasts about 3-4 days. Creatine kinase (CK) levels can be increased. Soreness can be generalized but usually resolves in several days. How to distinguish "ordinary" muscle soreness from statin-related effects can be difficult. The most commonly reported locations of statin-related symptoms are in the thighs and calves. The most commonly reported symptoms included heaviness, stiffness, or muscle cramps.

Extreme physical exertion can also trigger statin side effects. Patients who engage in more physical activity are more likely to suffer symptoms. This could be because a regular exercise regimen leads to low-level muscle inflammation, which in turn, magnified by statin therapy side effects.

Knowing your patients' baseline CK levels may be helpful. When evaluating muscle symptoms in patients taking statins, checking their CK levels should be considered. A CK level of 10 times the upper limit of normal should sound warning bells.

No Consensus on Muscle Inflammation Terminology

From myalgias to myopathy to myositis to rhabdomyolysis, there's a lot of confusion in the terminology with no consensus on definitions. Definitions vary from the American College of Cardiology (ACC)/ American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI), the National Lipid Association (NLA), and the FDA.

The June 2011 FDA Drug Safety Communication on simvastatin defines myopathy as "muscle pain, tenderness, or weakness, and an elevation of CK." Likewise, rhabdomyolysis is defined as "the most serious form of myopathy (that) can damage the kidneys and lead to kidney failure." Other sources further specify that in rhabdomyolysis, CK elevations are markedly elevated to at least 10 times the upper limit of normal. Fortunately, rhabdomyolysis is rare.

The Role of CK Levels in Managing Statin Side Effects

The decision on whether to check baseline "pretreatment" CK level is controversial. The NLA does not recommend checking baseline CK levels, but the ACC/AHA/NHLBI recommend a baseline CK level to aid in later clinical decision-making. Neither guideline recommends routine monitoring in asymptomatic patients. Some experts choose to stratify who should be screened with CK levels and recommend baseline CK levels for high-risk patients including older patents, patients on multiple medications (most of my internal medicine practice), and patients with impaired renal or hepatic function.

Checking CK levels can be confusing. There are many non-statin-related causes of elevated CK levels: vigorous exercise, hypothyroidism, alcoholism, trauma, seizures, and use of illicit drugs such as cocaine and amphetamines.

Additional Hints for Staving Off Muscle-Related Side Effects

Try every-other-day statin dosing. Alternate-day dosing is an option for reducing side effects especially for patients taking statins with long half-lives such as atorvastatin (half-life, 15 hours) and rosuvastatin (half-life, 20 hours).

Check for thyroid imbalance. Patients with uncontrolled hypothyroidism are at increased risk for muscle-related statin side effects.

Check vitamin D status. Anecdotal reports have found that some "statin-related" muscle side effects resolve with correction of vitamin D deficiency.

Consider coenzyme Q10. Several small clinical trials have suggested that coenzyme Q10 in doses of 100-200 mg/day can help prevent statin-related muscle side effects. More studies are needed to confirm this protective effect. Coenzyme Q10 is an antioxidant that helps stabilize membrane. It also has a role in mitochondrial function and...
Coenzyme Q10 is an antioxidant that helps stabilize membrane. It also has a role in mitochondrial function and adenosine triphosphate generation. Coenzyme Q10 supplements are considered to be relatively safe. Side effects include nausea, vomiting, diarrhea, pain, anorexia, allergic rash, and headache.[3,14]

Final Thoughts From the Statin Savvy Shopper

Experienced shoppers (like me) look for sales and “presales.” Generic simvastatin remains on the “sale” rack but now has style (dosing) concerns. Lipitor® is now on presale. Its patent is soon to expire, and it should be available in generic form in November 2011.[15] This means only good things for consumers when it comes to price. Cost of medication is a major barrier for many patients.

However, now there’s another interesting twist. Pfizer Inc.’s latest strategy is to obtain over-the-counter status for atorvastatin (Lipitor). Simvastatin has been available over the counter in the United Kingdom since 2004. However, the recent “simvastatin saga” will no doubt influence the FDA’s decision. The likelihood of success is also foreshadowed by previous failed attempts by Merck & Co., Inc. (lovastatin [Mevacor®]) and Bristol-Myers Squibb Company (pravastatin [Pravachol®]) for sister drugs.[16,17]

Not all statins are created equal, and the cheapest drug may not necessarily the best for your patients. Other statin manufacturers may also step up to the plate and lower their prices and try to “get part of the action.” When statin shopping, be sure to pick the right “size, style, and color” that is the best “fit” for your patients.

References

6. U.S. prescribing information for simvastatin revised to include new limits on the use of the highest dose -- 80 mg -- and updated drug interaction information [press release]. Whitehouse Station, NJ: Merck & Co., Inc.; June 8, 2011.


