STATIN'S SIDE EFFECTS

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BASED ON: UP TO DATE

FREQUENCY

Adverse reactions occur less frequently with the statins than with most other classes of lipid-lowering agents. Adverse muscle events remain important side effects. Hepatic dysfunction has been a source of concern; however, the actual risk appears to be very small.

In clinical practice, side effects with statins are common, which could be related in part to a heightened awareness adverse reactions traditionally attributed to the drug and treatment in patients with comorbidities that were often excluded from clinical trials.

There have been concerns that the more lipophilic statins (simvastatin, lovastatin, atorvastatin, and fluvastatin) may be associated with more adverse events than the more hydrophilic statins (pravastatin and rosuvastatin); however, fluvastatin (a lipophilic statin) appears to have a low rate of muscle side effects. Differences in adverse events may derive from heterogeneity in drug elimination pathways.

MANAGEMENT CONSIDERATIONS

As discussed before, while data from clinical trials suggest low rates of statin side effects leading to discontinuation, in clinical experience it is relatively common to find patients who are intolerant of one or more statins because of myalgias or other muscular symptoms. Less commonly, aminotransferase elevations require making changes in the statin, the statin dosage, or changes to another class of cholesterol-lowering therapy.

Options in patients with **aminotransferase elevations** (more than three times the upper limit of normal; confirmed on repeat testing) are similar, and include:

- Use of a different statin
- Dose reduction
- Alternate day therapy

Observational data suggest that, while discontinuation of statin therapy for side effects is relatively common, many patients tolerate the same drug or another statin when rechallenged. In addition, there may be risk associated with discontinuing statin therapy. Some patients do not tolerate statin therapy even after changing to a different statin, reducing the dose, and/or using alternate-day dosing.

HEPATIC DYSFUNCTION

Clinical studies of statins have demonstrated a 0.5 to 3.0 percent occurrence of persistent elevations in aminotransferases in patients receiving statins. This has primarily occurred during the first three months of therapy and is dose-dependent.

Rare episodes of more severe liver injury have also been seen, and one study suggested that these predominantly occur three to four months after initiation of statin therapy.

The pattern of more severe hepatotoxicity attributed to statins has included hepatocellular, cholestatic, and autoimmune injury.

In 2012, the US Food and Drug Administration (FDA) revised its labeling information on statins to only recommend liver function testing prior to initiation of statin therapy and to only repeat such testing for clinical indications. We and others agree that routine monitoring of liver function tests in patients receiving statin therapy is not necessary.

We recommend changing medications or lowering the statin dose in patients who are found to have an ALT level more than three times the upper limit of normal that is confirmed on a second occasion.

MUSCLE INJURY

Development of muscle toxicity is a concern with the use of statins.

Hypothyroidism is a potential cause of dyslipidemia, and hypothyroidism may predispose patients to statin-induced myopathy. As such, we suggest checking a thyroid-stimulating hormone level prior to initiating statin therapy.

RENAL DYSFUNCTION

Statins appear to be able to cause proteinuria through tubular inhibition of active transport of small molecular weight proteins, particularly in patients receiving rosuvastatin or simvastatin. However, it is believed that proteinuria with statins is a benign finding.

A large database study found an association between high potency statins and hospital admission for acute kidney injury, particularly in the first 120 days after initiation of statin therapy.

BEHAVIORAL AND COGNITIVE

Although concerns have been raised about increased suicide in patients treated with some lipid-lowering therapies, statins do not appear to be associated with an increased risk of suicide or depression.

Concerns have been raised in the media and popular press about cognitive dysfunction and memory loss associated with statin use. Although the analyses of adverse event reports does not show that statins cause memory loss, the apparently high rate of reports with lipophilic statins (simvastatin and atorvastatin) compared with hydrophilic statins (pravastatin) does suggest a possible biologic effect. Randomized trials of lovastatin and simvastatin have shown some evidence of minor decrements in cognitive function as measured by neuropsychological testing.

If an individual patient appears to have memory loss associated with lipophilic statin therapy (simvastatin, lovastatin, atorvastatin, or fluvastatin) and has a strong indication for lipid-lowering therapy, it would be reasonable to attempt treatment with a more hydrophilic statin (pravastatin or rosuvastatin).

DIABETES MELLITUS

It appears likely that statin therapy confers a small increased risk of developing diabetes and that the risk is slightly greater with intensive statin therapy than moderate statin therapy. As would be expected, given the evidence from clinical trials that statins reduce cardiovascular events in patient with diabetes, both randomized trials and observational studies suggest that the beneficial effects of statins on cardiovascular events and mortality outweigh any increased risk conferred by promoting the development of diabetes.

Statins could have effects on glucose metabolism that might influence the development of diabetes mellitus in nondiabetics or affect glycemic control in patients with existing diabetes.

OTHER POSSIBLE ASSOCIATIONS

- **Cancer** – There is no convincing evidence from meta-analyses of randomized trial that statins increase or decrease the risk of cancer.
- **Cataract** – Most large case-control and cohort studies, as well as a small randomized trial, have not found an increased risk of cataract, although large cohort studies from England, Wales, and the United States military health system have found that statin use was associated with an increased risk of cataract.
- **Neuropathy** – A number of case reports have suggested that statin use may be associated with the development of peripheral neuropathy. As such, a causal association between statin use and neuropathy remains possible but has not been proven.

- **Lupus** – There have been case reports of drug-induced lupus in patients receiving statins.
- **Androgen synthesis** – Some, but not all, studies suggest that statins may lower androgen levels in men, although it appears unlikely that this effect is clinically significant. Statins may also reduce androgen levels in women, including in women with androgen excess.
- **Immune response** – Some observational studies have suggested that the immune response to influenza immunization, and the efficacy of that immunization in preventing clinical influenza, may be reduced in older patients receiving statin therapy.

RISKS IN PREGNANCY AND BREASTFEEDING

In the United States, statins are rated category X in pregnancy, and the recommendation is to **discontinue** their use **prior to conception** if possible. The risk of statins in pregnancy remains uncertain; however, it appears that if statins are in fact harmful, the effect is likely relatively small.

Data on statin safety in breastfeeding are very limited. In the absence of adequate safety data, use of statins by breastfeeding mothers is discouraged.

THANKS FOR YOUR ATTENTION