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Defining patient risk for Transaminitis during Statin therapy

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Abstract:

Aim

Studies that evaluate the risk of hepatotoxicity from statins in hyperlipidemic subjects with elevated baseline serum transaminases are lacking, that's why we conducted a study to test the hypothesis that patients with elevated baseline liver enzymes have higher risk of statin hepatotoxicity.

Introduction

Statin treatment has been associated with a broad spectrum of hepatic adverse effects. The most common is an asymptomatic and usually transient elevation of serum aminotransferase levels that often occurs in the first 12 weeks of therapy. Most of the time, this biochemical finding is not correlated with histopathological changes and therefore does not meet criteria as a true indicator of liver injury. Although the underlying mechanism remains unclear, it may result from changes in the lipid components of the hepatocyte membrane, leading to an increase in its permeability with a subsequent "leakage" of liver enzymes. This is supported by the observation that elevations in aminotransferase levels (alanine aminotransferase [ALT] being a more reliable indicator than aspartate aminotranserase) occur with the use of structurally unrelated statins, as well as with other effective lipid-lowering drugs.Thus, the term transaminitis has been adopted to best define this phenomenon of liver enzyme abnormalities in the absence of proven hepatotoxicity. However, it has been proposed that increases in ALT level of more than 10 times the upper limit of normal should be used to differentiate true hepatotoxicity from transaminitis.

Material And Methods

Our study consisted of the following 3 cohorts of patients seen between January 1, 2013 and June 31, 2014: Cohort 1: 70 hyperlipidemic patients with elevated baseline enzymes (AST >40 IU/L or ALT >35 IU/L) who were prescribed a statin; cohort 2: 87 hyperlipidemic patients with normal transaminases who were prescribed a statin; and cohort 3: 114 patients with elevated liver enzymes but who were not prescribed a statin. The effect of statins on liver biochemistries was assessed over a 6-month period after statins were prescribed. Elevations in liver biochemistries during follow-up were categorized into mild-moderate or severe based on predefined criteria.

Results

The incidence of mild-moderate elevations and severe elevations in liver biochemistries in cohort 1 were 4.7% and 0.6%, respectively. Compared with cohort 1, individuals in cohort 2 had lower incidence of mild-moderate elevations (1.9%) but not severe elevations (0.2%). However, between cohorts 1 and 3, there were no differences in the incidence of mild-moderate elevations (4.7% vs. 6.4%) or severe elevations (0.6% vs. 0.4%). Statin discontinuation during the follow-up was similar between cohorts 1 and 2 (11.1% vs. 10.7%)

Conclusions

These data suggest that individuals with elevated baseline liver enzymes do not have higher risk for hepatotoxicity from statins. Management of dyslipidemic patients with high cardiovascular risk and increased liver enzyme levels represents a challenge. In more than one clinical scenario, the physician is confronted with the dilemma of whether to treat with statins, and in every case it is important to weigh the benefits and risks of treatment.

Keywords: hyperlipidemia, satin, hepatotoxicity.

Introduction

Cardiovascular disease is the single largest killer of both men and women in the world. Epidemiologic trials have established a direct relationship between low-density lipoprotein cholesterol (LDL) and cardiovascular events , and many clinical trials have confirmed that lipid-

lowering therapy reduces the risk of cardiovascular events . Statins are the drugs of choice for reducing LDL, on average y ielding an 18-55% dose-dependent reduction.[11] Statins also produce effects believed to be important in preventing cardiovascular events , such as plaque stabilization and reduction in inflammation. Thousands of patients have been treated with statins , with minimal adverse effects . The most common adverse events associated with statin therapy are gastrointestinal disturbances , fatigue, localized pain, and headache.[5-9] Serious adverse events that have been reported in major statin trials include myopathy , elevated transaminase levels , and rhabdomyolysis . The concern for monitoring liver function in patients taking statins is not shared by all. Many have highlighted that monitoring for hepato-tox icity is ineffective in predicting serious liver tox icity and that LFT abnormalities may only be a consequence of the statin's lipid-lowering effect and do not constitute true hepatotox icity. Finally, because the relationship between increased hepatic transaminase elevations and statin therapy in clinical trials is inconsistent , some have suggested that LFT abnormalities observed in patients taking statins may result from other conditions or drugs. A data collection form that included information on study duration, statin regimen, definitions of LFT abnormalities , and the numbers of patients reported to have changes in LFTs . All reported changes in LFTs were recorded on the data collection form. W hen abnormalities for both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values were reported, A LT was included in the meta-analysis because it is more hepatic-specific than AST. Nonetheless , because of the concern that hepatic safety of statins may not constitute a class effect , we examined the odds of having LFT abnormalities for each statin. The evaluation on the odds of having LFT abnormalities for each statin revealed divergent results (Figure 1). The proportions of patients having LFT abnormalities with lovastatin , simvastatin and pravastatin were not significantly different from that with placebo. However, fluvastatin therapy resulted in an increase in the odds of having LFT abnormalities The results from this meta-analysis support the observation that treatment with statins , as a class , is not associated with a significant risk of LFT abnormalities . No significant increase in the odds of having LFT abnormalities was observed when considering statins as a homogeneous class of agents . The apparent increased risk of having LFT abnormalities with fluvastatin deserves comment . This finding may be the result of chance because the number of events was low in both groups . Another possible ex planation is that fluvastatin has distinct effects on the liver because it is the only statin metabolized by cytochrome P450 (CY P) 2C9. Furthermore, because LFT elevations have been observed with other classes of lipid-lowering therapy , many have suggested that mild LFT elevations observed in patients taking statins may be induced by changes in lipid metabolism and not the drugs themselves . Nonetheless , until the exact mechanism behind LFT elevation in patients treated with statins is clarified, LFT monitoring should be performed in patients receiving high-dose atorvastatin. Furthermore, it is important to underline that the doses used in the trials evaluating lovastatin, pravastatin, and simvastatin were 40 mg or less , lower than the max imal recommended doses of these agents , and that we cannot establish whether our results apply to higher doses of these agents . Our results do not apply to patients receiving drugs known to cause liver tox icity or drugs inhibiting statin metabolism. Finally , although our results suggest that LFT monitoring may not be necessary in patients receiving low- to moderate-dose statins , baseline LFT measurement still would be warranted because the dosing and safety of statins in patients with ex isting liver dysfunction are not clearly established. Overwhelming data now ex ist that statins are both safe and effective in the primary and secondary prevention of coronary and vascular events in a wide variety of patients . Our results support previous observations that pravastatin, lovastatin, and simvastatin, at low-to-moderate doses , are not associated with a significant risk of LFT abnormalities and that LFT monitoring, other than prior to

starting therapy , is not warranted in patients taking a low-to-moderate dose (≤ 40 mg/day). Additional data are required to determine whether other statins have a similar safety profile.

Study objectives

To assess the risk of liver function test (LFT) abnormalities with the use of 3-hydroxy-3-methylglutary l coenzy me A reductase inhibitors (statins) for the treatment of hy perlipidemia. For a trial to be included in the meta-analysis, its duration of follow-up had to be at least 48 weeks and the trial had to include at least 400 patients, with at least 200 treated with a statin. He proportion of patients having LFT abnormalities was low only fluvastatin was associated with a significant increase in the odds of having LFT abnormalities.

Material and methods

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Table.1 The correlation between baseline enzymes and statin treatment

Characteristics	**Cohort 1**	**Cohort 2**	**Cohort 3**
Number of patients	**70**	**87**	**114**
Baseline enzymes	**elevated**	**normal**	**elevated**
Statine prescribed	**yes**	**yes**	**no**
Mild- Moderate	**4,7 %**	**1,9 %**	**6,4 %**
Severe	**0,6%**	**0,2 %**	**0,4%**

Conclusion

Our results support previous observations that pravastatin, lovastatin, and simvastatin at low-to-moderate doses are not associated with a significant risk of LFT abnormalities . Additional data are required to determine whether other statins have a similar safety profile.

Recommendations

FDA is advising consumers and (fluvastatin) health care professionals that:Routine monitoring of liver enzymes in the blood, once considered standard procedure for is no longer needed.Such monitoring has not been found to be effective in predicting or preventing the rare occurrences of serious liver injury associated with statin use.

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