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Review Article

The efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease

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ABSTRACT

Non-alcoholic fatty liver disease is an emerging liver disease in Western countries and the most frequent cause of incidental elevation of serum liver enzymes.

Dyslipidaemia is frequently observed in patients with non-alcoholic fatty liver disease, and treatment of dyslipidaemia plays a critical role in the overall management of these patients. Moreover, coronary artery disease remains the most common cause of death. Statins are effective lipid-lowering agents, associated with a lowering the risk of cardiovascular events in several interventional randomized clinical trials.

However, statins are often underused in patients with non-alcoholic fatty liver disease and many physicians are concerned about the prescription of statins to patients with unexplained persistent elevation of liver enzymes or active liver disease.

Based on currently available data, statin therapy, at low-to-moderate doses, seems to be safe and has low liver toxicity. Treatment of dyslipidaemia in patients with non-alcoholic fatty liver disease is recommended and may also improve liver function tests. In these patients, the risks of not taking statins could outweigh the risks of taking the drug. Conversely, the usefulness of statins for the treatment of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis is still a matter of debate and randomized clinical trials of adequate size and duration are required.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common and emerging liver disease in Western countries [1]. Fatty liver includes a wide spectrum of histological alterations ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), characterized by inflammation and fibrosis [2]. Therefore, NAFLD has been traditionally interpreted as a condition which may progress to liver-related complications such as cirrhosis, liver cancer, and liver mortality [3].

NAFLD is currently the most common cause of incidental abnormal liver tests and elevated serum liver enzyme activities in the developed world. NAFLD is regarded as the liver manifestation of the metabolic syndrome, as it is strongly associated with obesity, insulin resistance, hypertension, and dyslipidaemia [4], conditions associated with high cardiovascular risk. Patients with NAFLD have shown an increased risk for cardiovascular diseases, and coronary artery disease is the most common cause of death [5–7].

Statins are among the most-prescribed class of medications and increasing numbers of patients have received statins in recent decades in all developed countries. Over the last few years it has become possible to obtain simvastatin 10 mg over-the-counter in the United Kingdom and a potential increase in self-medication is predicted in other countries as well. Recently, the 2013 guidelines by the American College of Cardiology (ACC) and the American Heart Association (AHA) for the treatment of cholesterol expanded the indications for statin therapy for the prevention of cardiovascular disease [8]. As a consequence, it has been estimated that this would increase the number of adults who would be eligible for statin therapy by 12.8 million, with the increase seen mostly among older adults without cardiovascular disease [8].

Large scale, well-conducted, placebo-controlled, randomized clinical trials have established conclusive evidence that the

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Table 1
Statins and non-alcoholic fatty liver disease: highlights and open issues.

- Non-alcoholic fatty liver disease is the most common cause of incidental abnormal elevation of serum liver enzyme activities
- Non-alcoholic fatty liver disease is associated with dyslipidaemia and high risk for cardiovascular events
- Statins reduce the risk of major coronary and vascular events
- Statins are hepatically cleared and can cause elevations in liver biochemistries
- There is a concern that patients with underlying liver disease may be at increased risk for hepatotoxicity

long-term use of statins results in important reductions in the risk of experiencing major coronary and vascular events in patients with a wide range of lipid levels, both in primary and secondary prevention [9,10].

In primary prevention [10], statin treatment, compared with placebo, was associated with lower rates of all-cause mortality (relative risk [RR], 0.86), combined fatal and nonfatal cardiovascular disease (RR, 0.75), coronary heart disease events (RR, 0.73), and fatal and non-fatal stroke (RR, 0.78). Statins were also associated with reduced coronary revascularization (percutaneous coronary intervention and coronary bypass surgery) rates as compared to controls (RR, 0.62) [10].

This effect seems also to be dose-related as reported in a meta-analysis by Patti et al. [9] in which high-dose statin treatment significantly reduced periprocedural and 1-month cardiovascular events in patients undergoing percutaneous coronary intervention compared to no treatment/low-dose statin treatment (44% risk reduction).

Nevertheless, despite his proven efficacy, statin administration is sometimes limited by the concern about related side-effects, mostly due to muscle and liver injury.

Statins can cause elevations in liver biochemistries and there is a concern that patients with underlying liver disease may be at increased risk for hepatotoxicity (Table 1) [11]. All statins are cleared by the liver and their clearance depends on hydrophobicity (Fig. 1). The more hydrophilic compounds, as pravastatin, exhibit more pronounced active renal excretion, while the lipophilic compounds are mainly excreted by the liver (Table 2).

It has been also suggested that long term statin treatment may worsen hepatic histology in patients with NAFLD. Many physicians are concerned about the prescription of statins to patients with unexplained persistent elevation of liver enzymes or active liver disease, although the concern for monitoring liver function in patients taking statins is not shared by all. In fact, in a recent survey including 937 primary care physicians, only 50% would prescribe statins if the baseline liver alanine aminotransferase (ALT) values were 1.5 times the upper limit of normal (ULN) [12].

However, the majority of people who take statins tolerate them well and very few experience adverse effects. Occasionally, statin use could cause a mild rise in serum liver enzymes, which may rarely become severe and require treatment discontinuation. The exact mechanism by which statins cause ALT elevations is uncertain and liver damage is extremely rare. In fact, at currently recommended doses, an elevation of liver enzymes >3 times ULN, occurs in <1% of treated patients [13,14]. Moreover, it has also been highlighted that monitoring for hepatotoxicity is ineffective in predicting serious liver toxicity.

In this article we will review the available data from the international literature to summarize current evidence on the safety of the use of statins in patients with NAFLD.

2. Long-term statin treatment and liver toxicity

2.1. Liver toxicity of statins

Relevant statin-related liver toxicity is a rare but important adverse event occurring during statin treatment [15]. In fact, while asymptomatic elevations in serum ALT are relatively common in patients treated with statins [15], severe hepatic toxicity has been rarely described.

Data from the literature estimate an incidence of acute liver failure in patients exposed to statins similar to that of the general population (1:130,000 vs. 1:114,000) (Table 3) [16]. In a cohort of 270 patients undergoing liver transplantation for acute liver failure, only 3 of the liver recipients had acute liver failure attributed to a statin (2 to cerivastatin and 1 to simvastatin) over the 12-year study period [17].

During statin treatment, an asymptomatic elevation in ALT should not be considered a sign of ongoing liver disease or injury. The term of "transaminitis" has been proposed to describe the situation of liver enzyme leakage without hepatotoxic consequences [18]. Thus, "transaminitis" may explain many of the serum ALT elevations seen in patients treated with statins. There is general agreement that ALT is more useful than aspartate aminotransferase (AST) to reveal possible hepatotoxicity, as AST levels may increase either in muscle and liver injury. Moreover, ALT elevations should be confirmed in subsequent determinations, as a single ALT elevation is more suggestive for "transaminitis" than for liver damage. A possible effect of serum lipid lowering on the structure of cellular membranes has been hypothesized, allowing for more leakage of cellular enzymes [18].

Nevertheless, previous case reports reported that statin use may induce an autoimmune hepatitis [19–22]. In particular, Alla et al. [19] described three cases of autoimmune hepatitis after treatment with fluvastatin in two cases and atorvastatin in the third. Two similar cases were previously described by Pelli et al. [21] in a 65-year-old woman with primary hypercholesterolaemia treated with atorvastatin, and by Wolters et al. after rosuvastatin administration [22].

Table 2
Main pharmacokinetic characteristics of statins.

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Optimal time of dosing	Any time of day	Bed-time	With meals morning and evening	Bed-time	Any time of day	Evening
Absorption, %	30	98	31	37	50	65–85
t_{max}, h	2–4	0.5–1.5	2–4	0.9–16	3–4	1.3–2.4
$t_{1/2}$	11–30	0.5–2.3	2.5–3	0.8–3	20	1.9–3
Bioavaibility, %	12	10–35	<5	18	20	<5
Solubility	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Protein binding, %	>98	>98	96–98.5	43–54	88	>95
Primary metabolic pathway	CYP3A4	CYP2C9	CYP3A4	Glucuronidation – CYP3A4	CYP2C9–CYP2C19	CYP3A4
Hepatic excretion, %	>70	>68	>70	46–66	90	78–97
Renal excretion, %	2	6	30	60	10	13

Modified from Gazzerro et al. [11].