

Lipid-lowering therapies and liver enzymes

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Summary

Lipid-lowering drugs, especially HMGCoA reductase inhibitors, are widely used in the treatment and prevention of cardiovascular disease. They are generally well tolerated. The main, but uncommon, adverse effects of statins are myopathy and an increase in hepatic transaminases. This review focuses on concerns surrounding the safety of lipid-lowering therapy as it affects liver function. Asymptomatic statin-associated elevations in aminotransferases are common and dose-related, but they are not indicative of liver damage. Liver injury attributable to lipid-lowering therapies is very uncommon. Routine monitoring of liver function is not supported by the available evidence but is still recommended by the FDA. Decompensated cirrhosis, acute liver failure and significant cholestasis are contraindications for statin therapy, but not compensated chronic liver disease such as non-alcoholic fatty liver disease. Possible interactions (mainly with CYP3A4 inhibitors) deserve particular attention, and when statin therapy is needed the lowest effective dose should be prescribed in adults at risk for liver problems.

Key words: lipid-lowering therapies; statins; liver function tests

Introduction

The HMGCoA reductase inhibitors (statins) have been widely used in the treatment of hypercholesterolaemia, since they have been shown to reduce cardiovascular morbidity and mortality in patients at risk for coronary heart disease (CHD) and those with CHD. Lipid-lowering therapy is generally well tolerated and the risk of clinically significant hepatic injury is rare [1]. However, potential hepatotoxicity remains an important concern for the health care providers when more aggressive management of dyslipidaemia is increasingly recommended [2].

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Clinical case

BC is a 63-year-old male with a medical history of liver transplantation 6 months previously for liver cirrhosis after chronic hepatitis B 16 years before. He also has a history of hypertension, type 2 diabetes mellitus treated by insulin, and type IIa hyperlipidaemia. Recurrence of non-icteric liver cirrhosis (Child-Pugh A) related to chronic viral infection was established by biopsy of graft in 2003. He was very concerned by persistent high levels of total cholesterol.

Treatment of fluvastatin 80 mg daily was started in October 2005 due to persistent hypercholesterolaemia (CT 10.0, HDL 1.7, LDL 5.9, TG 1.8 mmol/l). One month later an increase in liver enzymes was observed (see fig. 1) and the fluvastatin treatment was discontinued. Despite dietary advice, plasma levels of total cholesterol remained elevated (8.2 and 8.6 mmol/l). In view of this patient's high cardiovascular risk a rechallenge with fluvastatin 80 mg/d was done three months later. Ezetimibe was then added and one year later fluvastatin was replaced by rosuvastatin 10 mg/d despite the increase in liver enzymes observed before statin therapy (fig. 1). During this period of statin therapy the patient's medication was the following: insulin, cyclosporine, valsartan, and lamivudine. A diagnosis procedure was performed to elucidate the cause of liver enzyme disturbances.

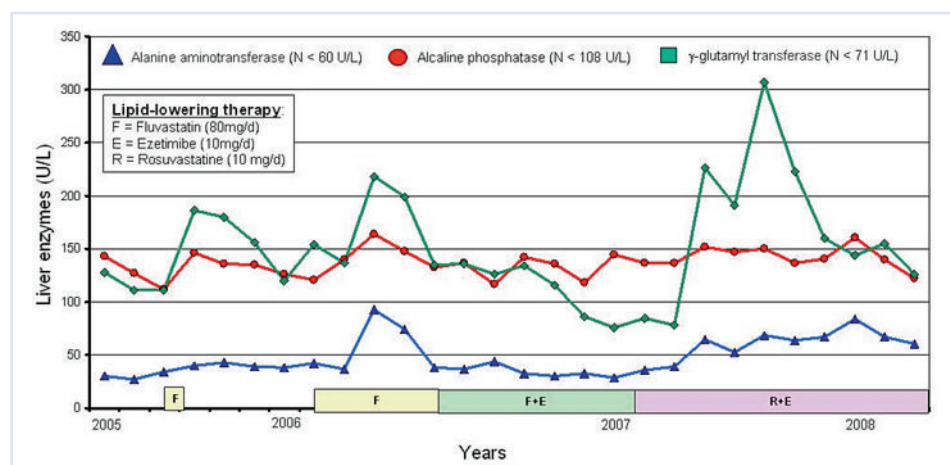
Treatment of dyslipidaemia and liver tests HMGCoA reductase inhibitors (statins)

The available statins exhibit major differences, including half-life, systemic exposure, maximum plasma concentration, bioavailability, protein binding, lipophilicity, metabolism, presence of active metabolites and excretion routes (table 1) [3]. The most common adverse effects of statins are gastrointestinal upsets, headache, rash and muscle aches: they are mild and transient. In the EXCEL study, a double-blind placebo-controlled trial evaluating the efficacy and tolerability of lovastatin, the incidence of these mild side effects was 1–15% including in the placebo group [4]. Statins rarely (ranging approximately from 1/10 000 to 1/100, table 2) cause clinically significant liver injury, even in patients with un-

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Figure 1
One case: Profile of liver enzymes observed from 2005 to 2008.



derlying liver disease [5]. The symptoms of hepatitis induced by statins include fatigue, sluggishness, anorexia and weight loss, and resemble those of an influenza-like syndrome. Most often the serum aminotransferases are only moderately elevated. If the treatment is discontinued, symptoms subside almost overnight but the serum aminotransferase concentration may not return to normal for several weeks, depending on the degree of elevation [6]. Clinically significant elevation of aminotransferases resulting in liver failure is extremely rare (based on case reports) and hepatotoxicity related to statin has certainly been overstated. Generally mild (ALAT 2–3×) aminotransferase elevation associated with statin occurs within the first 12 weeks, is asymptomatic and improves spontaneously. The incidence ranges from 0% to 3% (table 2). Rates of moderate to severe (ALAT >3×) elevation are low and have not been shown to differ significantly from placebo; the incidence of liver function test elevation is 1.1% in statin users versus 1.1% in placebo group [7].

In a cohort of more than 2 million Dutch residents Goettsch showed that the incidence of rhabdomyolysis, myopathy, acute renal failure and hepatic impairment in statin users was less than 1 in 3000 person-years' exposure to statins [8].

Non-alcoholic fatty liver disease (NAFLD)

As the prevalences of obesity and non-alcoholic fatty liver disease are rising, we are often faced with the decision whether to start a statin in patients with metabolic syndrome and baseline aminotransferase elevations. Before starting lipid-lowering agents, the cause of the liver enzyme elevation

should be investigated [9]. The most common differential diagnoses are viral hepatitis, alcoholic liver disease, haemosiderosis and autoimmune hepatitis. Serology, CDT, iron measurements, autoantibodies and echography may be necessary. Alpha-1-antitrypsin deficiency and Wilson's disease are also possible causes of chronic liver disease that may need to be ruled out in rare cases. The prevalence of NAFLD is 20% and the prevalence of its progressive form, non-alcoholic steatohepatitis (NASH), is 2–3%. Liver biopsy is the only way of definitely confirming or ruling out the diagnosis of NASH. It may progress to fibrosis and cirrhosis even in individuals who are not heavy drinkers. No specific therapy has been approved for this condition. Metformin,

thiazolidinediones, HMGCoA reductase inhibitors, antioxidants, pentoxifylline, lipoprotein lipase activators and low caloric diets have been tested without reaching any clearcut conclusion as to their benefits. Nevertheless there is increasing evidence that thiazolidinediones and medical and surgical treatments for obesity may confer a therapeutic benefit in NAFLD [10].

Risk factors for adverse effects of lipid-lowering agents

Risk factors for adverse effects of statins are summarised in table 3. The adverse effects of statins on liver are more common within the first 3 months of treatment and occur more often in association with advanced age and chronic illness [11], and at higher dosage.

Statin dose

In a meta-analysis of 9 trials, K. Dale reported a dose-related increased risk of elevated AST/ALT with statin therapy (risk ratio 3.1, 95% confidence interval 1.72–5.58 for high versus low intensity statin therapy) [12]. The frequency of aminotransferase elevation is 2/1000 patient-year with high doses and 1/1000 patient-year with low dose treatment [13]. In a retrospective analysis of data from 49 clinical trials, C. Newman found no differences between low-dose atorvastatin (10 mg) and placebo, but a slightly increased rate with high dose atorvastatin (80 mg) when examining AST/ALT elevation [14]. Analysing adverse events reported in 23 treatment arms in large prospective randomized statin trials, A. A. Alsheikh-

Table 1
Pharmacokinetics of HMGCoA reductase inhibitors.

Drug	Metabolism	T1/2 (h)	Protein binding (%)	Metabolites	Urinary excretion (%)	Faecal excretion (%)	Lipophilicity
Atorvastatin	CYP3A4	15–30	90	Active	2	70	Yes
Simvastatin	CYP3A4	2–3	95	Active	13	58	Yes
Pravastatin	Sulfation	1–2	50	Inactive	20	71	No
Fluvastatin	CYP2C9	1–3	99	Inactive	6	90	Yes
Rosuvastatin	Minimal by CYP	20	88	Active	10	90	No

Adapted from [11, 34, 40].

Table 2
Incidence rate of liver enzyme increase (>3× ULN or >120 U/l) in participants of randomised controlled trials of statins.

Trials	Participants (N)		Type of statins	Duration (yr)	Single measure (%)		2 consecutive measures (%)	
	Statin	Placebo			Statin	Placebo	Statin	Placebo
HPS	10269	10267	Simva	5.3	0.4	0.3	0.1	0.0
EXCEL	6582	1663	Lova	0.9	1.4	0.9	0.7	0.1
ASCOT	5168	5137	Atorva	3.3				
LIPID	4512	4502	Prava	6.1	2.1	1.9		
AFCAPS/ TexCAPS	3304	3301	Lova	5.2			0.5	0.3
WOSCOPS	3302	3293	Prava	4.9	0.5	0.4		
PROSPER	2891	2913	Prava	3.2	0.0	0.0		
4S	2221	2223	Simva	5.4	2.1	1.4	0.6	0.5
CARE	2081	2078	Prava	5.0	3.2	3.5		
MIRACL	1538	1548	Atorva	0.3	2.5	0.6		
LIPS	844	833	Fluva	3.9			1.2	0.4
GREACE	800	800	Atorva	3.0				
PMSG	530	532	Prava	0.5	1.1	0.2	0.0	0.0
ACAPS	460	459	Lova	3.0	1.3	1.3		
REGRESS	450	434	Prava	2.0	0.0	0.2		
FLARE	409	425	Fluva	0.8	1.7	0.7	0.0	0.0
KAPS	224	223	Prava	3.0	1.8	1.3		
LRT	203	201	Lova	0.5	1.5	0.5		
MAAS	193	188	Simva	4.0	0.0	0.0		
Riegger et al.	187	178	Fluva	2.5	0.0	0.0		
LCAS	157	164	Fluva	0.9			1.3	0.0
Total	46355	41362						
Incidence per 1000 person-yr	82411	72457			3	2	1.1	0.4

Where no data, no increase in liver enzymes.
Adapted from [13].

Table 3
Risk factors for adverse effects of statins.

High dose
Advanced age and chronic illness
More common within the first 3 months
Drugs:
Cytochrome P450 3A4 inhibitors: antibiotics, antifungal drugs, antidepressants, protease inhibitors, antiarrhythmics, immunosuppressive drugs
Cytochrome P450 2C9 inhibitors: antifungal drugs
Other lipid-lowering agents: niacin, fibrates (gemfibrozil> bezafibrate=fenofibrate)
Adapted from [11].

Ali found that drug and dose-specific effects were more important determinants of liver toxicity than magnitude of LDL lowering [15]. From a pooled analysis of all statin New Drug Application Data, it is clear that the highest doses of statins have higher rates of transaminase elevation, but that there is

no correlation between a persistent increase in aminotransferases and statin-induced lowering of LDL [16].

Hydrophilicity

In his meta-analysis, K. Dale found that higher intensity hydrophilic statin therapy may increase the risk of elevated AST/ALT (RR 3.54 [95% CI, 1.83–6.85]), but not higher intensity lipophilic therapy (RR 1.58 [95% CI, 0.81–3.08]). However, this meta-analysis was based on limited trial data (only 9 trials included), rosuvastatin was not included (only pravastatin as hydrophilic) and no clear physiological explanation was provided. It is not certain that this was a real effect rather than a chance finding. Statin dosage is probably a more important factor, as described above.

Drug interaction (table 4)

Hepatotoxicity is more common among patients receiving drugs that are metabolised by the cytochrome P450 enzyme systems [11]. Studies compared the interaction profiles of pravastatin, simvastatin and atorvastatin when co-administered with cytochrome P450 3A4 inhibitors in healthy subjects: comparing with pravastatin alone, co-administration of

pravastatin with verapamil or itraconazole found no significant change in pravastatin pharmacokinetics. However, concomitant verapamil increased the simvastatin concentration, itraconazole the atorvastatin concentration and clarithromycin all three statins' concentrations [17]. With the exception of pravastatin (transformed enzymatically into liver cytosol) and rosuvastatin (minimal cytochrome metabolism),

Table 4

Common drugs that may interact with statins.

Drugs that may increase statin concentration
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)
HIV protease inhibitors (lopinavir, ritonavir, saquinavir, amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, tipranavir, darunavir)
Azole antifungals (itraconazole, ketoconazole, miconazole, posaconazole, voriconazole)
Diclofenac
Nefazodone
Calcium antagonists (diltiazem, verapamil)
Amiodarone
Cyclosporine, tacrolimus
Drugs whose concentration may be increased by statin
Digoxine
Coumarin anticoagulants*
Oral contraceptives
Drugs with similar side effects
Fibrates (gemfibrozil>bezafibrate=fenofibrate)
Niacin
* INR increased by about 0.3.
Adapted from [11].

Table 5

Monitoring of liver function tests with statin therapy.

National Lipid Association Statin Safety Assessment Task Force [9]:
If ALAT <3x: no need to discontinue statin
If ALAT >3x: repeat test, find aetiology, ↓dose or change therapy
Bilirubin better indicator of liver injury than aminotransferases
Liver Expert Panel [30, 32, 33]:
Asymptomatic increases in ASAT & ALAT: class effect of statin, uncommon liver dysfunction
No routine monitoring of LFTs, measure only if risks (chronic hepatitis, OH, interaction)
Statins can be used in patients with NAFLD or NASH
Chronic liver disease and Child's A cirrhosis: not a contraindication for statin use
Contraindication for statin: decompensated cirrhosis or acute liver failure or significant cholestasis
FDA:
Initial LFTs, then 2–12 weeks and every 6 months and at any drug increase
Inform patients of possible drug–drug interactions

all statins undergo metabolism by cytochrome P450 (table 1). Theoretically all drugs that inhibit cytochrome P450 3A4 may increase the serum concentration of atorvastatin and simvastatin, and drugs that inhibit cytochrome P450 2C9 may increase the concentration of fluvastatin. It is suggested that cyclosporine may interact with statins via mechanisms not limited to CYP450 3A4 inhibition, since an increase in pravastatin bioavailability has been reported in its presence [11]. In the ALERT trial, fluvastatin was shown to be very safe in renal transplant patients receiving cyclosporine [18]. However, severe adverse effects, such as rhabdomyolysis, have also been reported from statins not metabolised by cytochrome P450 [19]. Although theoretically plausible, the clinical relevance of these differences between statins is uncertain.

Differences between lipid-lowering agents for effects on liver

Statins

Irreversible liver damage leading to death or liver transplantation appears to be extremely uncommon with statins [5]. Asymptomatic elevation of aminotransferases under statins has been found in trials but does not necessarily indicate hepatic damage, especially when seen in the setting of a normal bilirubin level (without significant cholestasis) [9]. The increase in transaminases is a dose-related phenomenon and the degree of elevation does not reflect the amount of liver injury [20]. Clinically significant acute liver injury is very rare and may be seen in combination with other medications. Fulminant hepatic failure is extremely rare and estimated to be 2 in one million. Autoimmune hepatitis may be induced in genetically susceptible individuals (case reports). The rate of acute liver failure associated with lovastatin is one per 1–1.1 million patient-treatment years, which is the same as the background rate of idiopathic acute liver failure [7].

Niacin

Nicotinic acid is used primarily to increase HDL. Acute hepatic failure has been reported [21], but is very rare. The typical pattern of injury involves elevation of aminotransferase levels although a mixed pattern of hepatocellular and cholestatic injury can be seen. This potential hepatotoxicity is common with sustained-release formulations (SR) but rare with immediate-release or extended-release (ER). The increase in liver toxicity with SR niacin chiefly occurred with doses >1500 mg/day. In contrast to dietary-supplement SR niacin formulations, an ER formulation available only on prescription has shown a notable rarity of hepatotoxicity in large clinical trials submitted to the US Food and Drug Administration (FDA) [22].

Fibrates

Some case reports have found that gemfibrozil results in cholestatic hepatitis and other rare reported cases of hepatocellular injury [23]. Fenofibrate was reported to be potentially involved in a case of hepatitis and fibrosis that was possibly increased due to use in combination with statins [24]. As a general rule, high doses of statin should be avoided in patients who are taking a fibrate. The risk of fibrate toxicity is higher in patients with impaired renal function, because these drugs are largely excreted by the kidney.

Ezetimibe

This drug inhibits intestinal absorption of cholesterol, but it enters the circulation and some authors found that it may in rare cases cause hepatotoxicity in the form of severe cholestatic hepatitis and acute autoimmune hepatitis [25]. In some case reports it was noted that the frequency of increased transaminases was potentially higher in patients receiving ezetimibe when associated with statins [26].

Combinations

Combination therapy of statins and fibrates may be needed to treat mixed hyperlipidaemia. In a meta-analysis covering 36 clinical trials and 29 case reports, A. Shek found that this combination increased the risk of myopathy but was unable to conclude on an elevated risk of hepatotoxicity [27]. The combination of statin and gemfibrozil is contraindicated; in a retrospective observational study using an administrative claims database, M. J. Cziraky showed that this association increases the relative risk of hepatic adverse medical events [28]. The FIELD study [29], despite its mixed results concerning the effect of fenofibrate on cardiovascular outcomes in individuals with type 2 diabetes, found that fenofibrate was well tolerated when used alone or in combination with statin. ACCORD includes a treatment arm with combined treatment of atorvastatin and fenofibrate in diabetic patients. The results, expected in the next few years, will certainly be of help in balancing the risks and benefits of such a combination in this high cardiovascular risk population.

When to measure liver function tests?

There is controversy on whether to do initial laboratory tests and monitoring in patients receiving statins (table 5). For hepatologists, statin-associated elevations in aminotransferase levels are not indicative of liver damage or dysfunction, and liver function tests should not be monitored in patients receiving long-term statin therapy [30]. The FDA still recommends initial measurements before therapy, after 2 to 12 weeks of treatment and every 6 months during long-term treatment and at any drug increase [31]. A more common approach is to measure aminotransferases, especially when there is increased risk for the liver, i.e., chronic hepatitis, excessive alcohol consumption or potential drug interaction [32]. Baseline values may also be useful for the purpose of comparison. Routine monitoring probably adds little information when prescribing low doses in otherwise healthy individuals not taking multiple medications, but it is probably more useful to test when symptoms occur. In the case of hepatotoxicity many adverse reactions are cholestatic, generally benign and, due to pruritus or jaundice, easily detected before serious liver injury occurs. Patients should be aware of possible drug to drug interactions and the physician's judgment must prevail in regard to monitoring [33]. If an aminotransferase increase occurs under statin therapy, it is recommended that the reason first be found, knowing that it is not always drug induced. If ALT is more than 3 times the baseline value

on two different blood tests, it is recommended that the dose be lowered or the therapy changed [34]. The National Lipid Association Statin Safety Task Force made a list of recommendations for the monitoring of liver, muscle and kidney toxicity in statin users, based on a review of data from numerous different sources [9]. Regarding the liver, their cautious recommendation was to continue routine liver function monitoring until there is a change in the FDA-approved prescribing information for statins for medico-legal issues.

Use of statins in chronic liver disease

The data regarding the use of statin in chronic liver disease are limited, but several recent studies have investigated whether patients with underlying liver disease are at increased risk for statin hepatotoxicity. Investigators have recently shown that patients with chronic hepatitis C are not at higher risk for statin hepatotoxicity than hyperlipidaemic patients with no hepatitis [35]. In a trial comparing pravastatin 80 mg or placebo in patients with chronic liver disease (NASH or hepatitis C), the rate of aminotransferase elevation was low in the group receiving pravastatin and not different from placebo, and none of the patients had an exacerbation of their underlying liver disease [36]. Another study showed that hyperlipidaemic individuals with elevated baseline liver enzymes did not have a higher incidence of simvastatin or atorvastatin hepatotoxicity than those with normal liver enzymes [37]. Emerging data even suggest that statin may confer benefits in patients with underlying liver disease, such as NASH [38].

One issue in clinical practice is that patients with underlying liver disease exhibit regular fluctuations in their liver tests, and it may therefore be very difficult to determine whether the cause of the variation in liver function tests is the underlying liver disease or the lipid-lowering medication.

In the case of liver disease the recommendation is to avoid statin therapy in patients with significant cholestasis, acute liver failure or decompensated cirrhosis [30]. Child's A cirrhosis is not a contraindication to lipid-lowering therapy, and statins can be used in NAFLD and NASH. Indeed, patients with NAFLD may benefit from statins due to their high risk of cardiovascular disease [39]. In the case of chronic liver disease and dyslipidaemia, if the patient can completely abstain from alcohol a low dose statin may be used and, if necessary and with appropriate caution, combined therapy [36].

Back to the case

The evolution of the liver enzymes under lipid-lowering therapy was marked by episodes of acute elevation of gamma GT, although without significant worsening of alkaline phosphatase and transaminase (figure 1) or elevation of bilirubin levels, in the absence of alcohol

abuse. Without changes in treatment the liver enzymes returned to a level similar to that in 2005 before the introduction of fluvastatin. For these reasons there was little evidence of drug toxicity. In 2008, liver biopsy confirmed the liver cirrhosis (Child-Pugh A) of the graft, with only mild signs of inflammation. CT scan in 2008 revealed the presence of occlusive thrombosis of the portal vein. In the absence of other common causes of gamma GT elevation, such as alcohol abuse, new viral hepatitis or NASH, we assumed that this transient worsening was related to acute occlusive portal vein thrombosis. Anticoagulation with warfarin was started immediately. Under lipid-lowering therapy the LDL-cholesterol levels oscillated between 2.5 and 3.4 mmol/l.

A case of this nature suggests that in the presence of liver disease drugs must be introduced with caution. In this case of hypercholesterolaemia, combined with other cardiovascular risk factors in a diabetic patient, the role of the clinician is to evaluate the risk–benefit ratio of lipid-lowering therapy in the light of the available scientific data. Further, the worsening of liver parameters should not be immediately interpreted as adverse effects of statins, but should drive a diagnostic search for its aetiology. Finally, according to current scientific evidence statin therapy should not be regarded as contraindicated in patients with chronic liver disease or compensated liver cirrhosis. However, strict clinical and biochemical monitoring of therapy is required and counselling by specialists recommended.

Conclusion

In many cases elevation of aminotransferase levels under statins is not indicative of liver damage or dysfunction, but related to other causes such as NAFLD, NASH or viral hepatitis. This elevation of liver enzymes is correlated with dose. In some cases statin therapy has been reported to increase the risk of dramatic liver effects such as acute liver failure and death, but this is an extremely rare complication, uncommon and often asymptomatic. Liver function tests should not be routinely monitored in patients receiving long-term statin therapy. If NAFLD, NASH, compensated cirrhosis and chronic liver disease are not contraindications for statin therapy, significant cholestasis, acute liver failure or decompensated cirrhosis are. The best options in reducing the risks of adverse liver effects are caution in patients at risk of liver dysfunction, in particular with statin dose, observance of contraindications for the use of lipid-lowering agents, and careful attention to drug interactions.

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