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Statins in hepatobiliary diseases : effects, indications and risks

Ine Lowyck, Johan Fevery

Department of Hepatology, UZ Gasthuisberg, Leuven

Abstract

Background and study aims : **Statins are among the most frequently used medications. Our aim was to study their indications or contraindications in hepatobiliary diseases.**

Patient and Methods : **This study was stimulated by a patient with PBC, marked hypercholesterolemia and cardiac problems.**

Results : **Besides a lipid lowering effect, statins have other benefits, such as prevention of arterosclerosis, reduction of the risk of developing diabetes and inhibition of fibrogenesis. The effects depend on the type of statin, the genetic and acquired characteristics of the patient and the interaction with other medications. Side effects such as myopathy and liver toxicity are rather rare but should be monitored. The use of statins in liver disease is not clearly defined. Hyperlipidaemia is a risk factor for arteriosclerosis in NAFLD (Non Alcoholic Fatty Liver Disease), but fibrates might constitute the treatment of choice. Preliminary data suggest that biochemical and histological improvement in NAFLD might be obtained with atorvastatin or pravastatin. The use of statins in the medical therapy of gallstones remains unclear. Combination therapy might have a beneficial effect in cases of stones with mixed composition. Patients with Primary Biliary Cirrhosis or with chronic cholestasis in general have high HDL-cholesterol levels but a large amount of Lipoprotein X particles, which have a protective effect. As such, statin therapy is often not really indicated.**

Conclusion : **When cardiovascular problems arise in patients with chronic cholestasis, an underlying factor should be looked for. The lipid abnormalities depend also on the stage of the PBC.** (Acta gastroenterol. belg., **2007**, 70, **381-388**).

Key words : statins, PBC, cholesterol.

Introduction

Statins or HMG CoA reductase inhibitors are currently often prescribed. Side effects are uncommon, but should be known and be recognised at an early stage. There are differences between the several statins regarding both effects and side effects. Their main purpose is treatment of hyperlipidemia, but we wondered whether they could also be useful in hepatobiliary diseases such as chronic cholestasis e.g. primary biliary cirrhosis (PBC) or in non alcoholic steatohepatitis (NASH) and in gall stone disease ? We will first present a patient with primary biliary cirrhosis with hypercholesterolemia, with the question if hypercholesterolemia in such patients creates an increased cardiovascular risk. Later on, we will discuss other indications or effects of statins and their potential hepatic side effects.

Case report

This female patient was 42 years old when PBC stage II was diagnosed. Fourteen years later, she developed signs of ischemic heart disease and hyperlipidemia was documented (Table 1), although she had marked steatorrhea (28,5 g fat/24 hrs). A PTCA with coronary stenting of the LAD was done. Four years later, because of chest pain, a new PTCA showed a 60% stenosis of the proximal RAC, which was also stented. Because of severe cholestatic pruritus, cholestyramine (✗Questran) was prescribed. She received a liver transplant one year later because of worsening of her general condition with progressing cholestasis and marked pruritus.

Table 1. — **Lipid values of our patient taking in Questran**

	1996	1997	Normal values
Cholesterol mg/dl	474	541	< 190
HDL mg/dl	90	54	> 40
LDL mg/dl	362	470	< 115
VLDL mg/dl	22	17	< 30
Total cholesterol/HDL ratio	5.3	10	< 4.75

Question

Do patients with PBC have an increased cardiovascular risk due to hypercholesterolemia ? Are statins or other lipid lowering therapies of any value in this situation ?

Discussion

1. *The various actions of statins*

The main effect of statins is a lipid lowering effect, but besides that, there are some so-called pleiotropic effects targeting other organs. Some of these effects are still subject of experimental research, others are under clinical evaluation.

1.1. Lipid lowering effect

Statins are reversible inhibitors of HMG (3-hydroxy-3-methylglutaryl) CoA reductase, a key enzyme in the synthesis of cholesterol. They bind to the enzyme and competitively take the place of the cholesterol precursor

Corresponding to : Johan Fevery, Hepatology, UZ Gasthuisberg, B-3000 Leuven. E-mail : Johan.Fevery@med.kuleuven.be
Ine.Lowyck@uz.kuleuven.be

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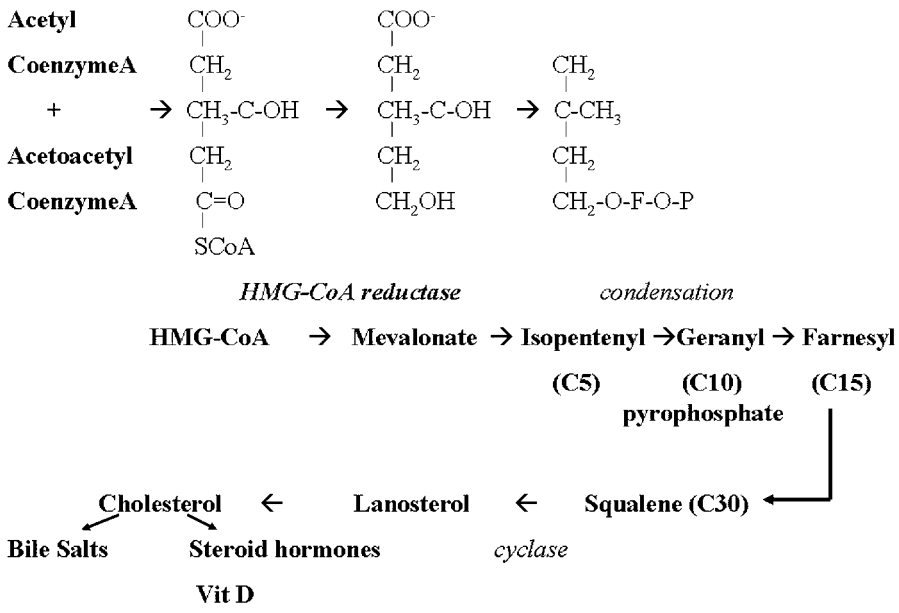

Fig. 1. — Scheme of Cholesterol production

HMG-CoA (Fig. 1). As a result, less mevalonate and eventually less cholesterol will be produced. The main effect of statins is lowering the LDL in circulation. This is a consequence of an increased expression of LDL-receptors at the level of the liver cell membrane in response to the decreased hepatic production of cholesterol. As a result of the increased LDL-receptors, more LDL-cholesterol is taken out of the circulation, and less LDL-particles are released in circulation (1). An additional effect can be seen in a shift in the LDL subfractions, creating less atherogenic LDL-particles (2). Another, though less important effect, is an increase of HDL and a decrease of serum triglycerides. An additive lipid lowering effect can be created by the combination of statins with resins or with the cholesterol absorption inhibitor Ezetimibe (✗ Ezetrol) (3).

1.2. Effect on the vessel wall

The benefits of statins in primary and secondary prevention of coronary atherosclerotic damage are proven (4-5), but the mechanism of action is not yet entirely understood. In fact, atherosclerotic regression only occurs in a minority of the patients, and in those patients, the positive effect of statins is seen already within 6 months, a period in which atherosclerotic regression is almost impossible. There might thus be other mechanisms involved, such as a plaque stabilizing effect, reversal of endothelial dysfunction, decreased thrombogenicity and reduced inflammation (see reduction in CRP as discussed below), though these issues are all rather hypotheses than proven facts (6).

1.3. Diabetes mellitus

The WOSCOPS study concerning primary prevention in men with hypercholesterolemia surprisingly found that therapy with pravastatin reduced the risk of developing diabetes by 30%. The underlying mechanism is not yet known (7).

1.4. Possible inhibition of development of fibrosis in general and of liver fibrosis

In studies with isolated hepatocytes, statins inhibit the expression of the fibrosis inducing Connective Tissue Growth Factor (CTGF), slowing down, for example, the development of liver fibrosis (8). Liver fibrosis mainly results from collagens and other substances released by activated hepatic stellate cells, and this is aggravated by the existence of an amplifying vicious circle since. On the other hand, recent studies showed that activated stellate cells also secrete angiotensin II, which stimulates further development of fibrosis. Therefore, blockade of the Renin-Angiotensin system by angiotensine converting enzyme (ACE) inhibitors would e.g. by sartanes was shown to slow down liver fibrosis (9-10), and. In addition, co-administration of pivastatin was shown to enhance the antifibrogenetic effect of candesartan in the CCL4 model of liver fibrosis in rats (11).

1.5. Decrease of intrahepatic portal resistance

Portal hypertension in the liver occurs partly due to mechanical factors (fibrosis, nodules…) but also partly because of increased vasoconstriction due to an imbalance between a low NO (nitric oxide) concentration in the liver (which is the strongest vasodilatator) and an increased concentration of vasoconstrictors (12). Van de Casteele *et al.* (13) found that an increase of intrahepatic NO, as result of gene therapy with an adenovirus encoding for endothelial NO synthase lowers the high portal pressure (13). Statins seem to increase the hepatic NO concentration, resulting in a decrease of the

hepatic resistance (and as consequence a decrease of portal hypertension) in cirrhosis (14).

1.6. Potential effects on bone tissue

In some clinical studies a decrease of bone fractures was seen in patients on statin therapy. This suggested a potential beneficial effect on osteoporosis. Meanwhile, experiments showed that statins increase the expression of bone morphogenetic protein 2, a strong stimulator of osteoblast differentiation and activity. They also augment the mineralisation of osteoblasts in culture (15,16). Other researchers (17) could prove a dose dependent decline of differentiated osteoclasts. Thus in general, statins seem to have an anabolic effect on bone tissue. Chronic intake of statins by ovariectomised rats caused an increase of bone density (BMC). Not all the studies, however, showed a positive effect on bone tissue. A possible explanation could be that statins mainly act on the liver, have a low bioavailability and a low distribution in bone tissue. To be more effective in bone tissue, a new kind of statin should be developed, which is bone specific and has a bone targeted drug delivery.

1.7. Statins, nitric oxide and C-reactive protein (CRP)

Serum levels of C-reactive protein (CRP) are increased in inflammation and CRP is implemented as a predictor of arteriosclerosis (18). CRP is produced in the liver and an increase of synthesis occurs in case of inflammation. Statins have a CRP lowering effect, but does this also mean that inflammation is suppressed ? Voleti and Agrawal (19) searched for the regulation of the CRP gene encoding for the CRP protein. Pravastatin and simvastatin suppressed the induction of the CRP expression in human hepatoma cells when these were stimulated by pro-inflammatory cytokines IL-6 and IL-1 beta. Nitroprusside, a nitric oxide (NO) donor, had a similar effect, despite the fact that the inflammatory reaction remained present because of the presence of the CRP-inducing cytokines IL-6 and IL-1 beta. The effect of NO and statins on CRP levels seems thus to be a result of suppression of transcription of the gene to the protein with ensuing suppression of the production of the CRP protein.

According to this information, a decrease of CRP seen during therapy with statins doesn't necessarily mean that the (arteriosclerotic) inflammation has decreased. Therefore measuring CRP during statin or NO therapy becomes of little importance for the in vivo process (19).

1.8. Potential inhibition of carcinoma growth

Mevalonate is derived from 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), and is further metabolised to geranyl- and farnesyl pyrophosphate (GPP and FPP), both precursors of the sterols. But the geranyl- and farnesyl group of GPP and FPP can covalently bind to proteins, and in particular to small G proteins (GTPases) such as Ras and Ras-related proteins, which play an important role in malignant transformation of cells. Farnesyl prenyl transferase (FPTase) and geranylgeranyl prenyl transferase (GGPTase) inhibition are used in chemotherapy. Currently preclinical investigations are carried out with farnesyl transferase inhibitors, geranylgeranyl transferase inhibitors, dual inhibitors, biphosphonates, histone deacetylase inhibitors and other compounds. Inhibiting HMG-CoA reductase with statins seems to reduce geranyl and farnesyl, which means malignant transformation could be slowed down. Clinical trials will have to confirm their clinical use in this setting (20).

It has also recently been found that mevastatin and simvastatin augment the intracellular accumulation and cytotoxicity of doxorubicin in human malignant mesothelioma (HMM) cells. Normally these cells are resistant to multiple chemotherapeutic agents, such as doxorubicin, because they constitutively express P glycoprotein and multidrug resistance associated protein 3 (MDP3), which are transport proteins pumping this medication quickly out of the cells. Statins are thought to inhibit this function. This effect of statins is nitric oxide (NO) dependent, since it doesn't occur in the presence of an NO synthase inhibitor or an NO binding system (21). Similar tumour suppressive effects were described by Paragh *et al.* (22), who examined rats after inoculation of hepatocellular tumor cells beneath the left renal cortex. They showed that pre-treatment with 2 or 20mg/kg/day of fluvastatin had a dose dependent inhibitive effect on tumour growth.

1.9. Beneficial effect on renal podocyte function with improvement of impaired renal function in rats with glomerulonephropathy.

When fluvastatin was given to rats with puromycine aminonucleoside induced nephrotic syndrome, a significant decrease of proteinuria was seen. Both immunofluorescence studies of the podocyte associated proteins nephrine and podocine, and electron microscopy showed a better podocyte function in rats under treatment with fluvastatin (23).

1.10. Effect on Vit D levels.

Since 7-dehydorcholesterol is also the precursor of Vit D_3 formation, one could expect that suppression of the cholesterol formation by statins might lead to a decrease in Vit D_3. However, a recent study in 83 patients documented rather a slight increase in serum 25-hydoxycholecalciferol levels following treatment for 12 months with various doses of atorvastatin (24). The mechanisms is still unclear but at least this effect is reassuring.

2. *Effects of statins*

The effect of statins is variable and does not only depend on the specific statin (lipophylic characteristic, absorption, protein binding, etc), and the dose, but also on patient specific factors such as genetic determinants and interfering medication (5,25).

Table 2. — **Characteristics of the different statins**

Origin	Pravastatin fungi	Simvastatin fungi	Atorvastatin synthetic	Fluvastatin synthetic	Rosuvastin synthetic
Max dosis (mg/dag)	40*	40	80	80	40 mg
LDL Chol reduction	34%	41%	50-60%	24%	63%
Serum TG-reduction	24%	18%	29%	10%	28 %
Plasma half-life	1-2 h	1-2 h	14 h	1-2 h	19 h
Penetration in CNS	no	yes	No	no	
Renal excretion of absorbed dose	20%	13%	2%	6 %	10 %
Hepatic metabolisation	Sulphated	CYP 3A4	CYP 3A4	CYP 2C9	Minimal
Are inhibitors of		CYP 2C8 and 3A5	CYP 2C8 and 3A5	CYP 2C8	
Binding to proteins	50%	95-98%	98%	> 98%	90%
Lipophilic	little	yes	yes	yes	little
Active metabolites	no	yes	yes	no	no

* 80 mg has been studied, is safe and causes an LDL reduction of 38 to 39% (54) ; the approved dose however is 40 mg.

2.1. Mutual differences between statins

The different statins currently available on the Belgian market are atorvastatin (brand name Lipitor), fluvastatine (brand name Lescol), pravastatine (brand name Prareduct, Pravasine), simvastatine (brand name Zocor) en rosuvastatine (brand name Crestor) (Table 2). Different effects have been noted on :

- LDL : atorvastatin and rosuvastatin seem to cause the highest LDL cholesterol reduction (30% to 65%) (26,27).
- HDL : simvastatin and rosuvastatin appear to reach the most significant elevation of HDL cholesterol (28).
- Triglycerides : Rosuvastatin causes the largest triglyceride decrease (26,1% with a dose of 40 mg) (27). Atorvastatin is less potent than rosuvastatin, but still has more effect than simvastatin. This effect is dose dependent (29).

2.2. Patient-specific factors

Genetic determinants can influence the effects and the potential side effects of the different statins because the degree and rate of metabolisation are genetically determined. When mutations occur in the gene encoding for the CYP 2D6 enzyme or when combining medication has an inhibiting or inducing effect, an altered effect of simvastatin is seen (30). In patients with homozygous familial hypercholesterolemia, statins don't have any effect, because these patients can't make any functional LDL receptors. Except for atorvastin and rosuvastatin, the best moment for intake of statins is in the evening, because of the diurnal rhythm of cholesterol synthesis, producing more endogenous cholesterol in the evening (1). Pravastatin should be taken during the meal since absorption is much higher in combination with food intake. The absorption of other statins is not significantly influenced by food intake.

3. *Side effects of statins*

Statins are generally well tolerated . Minor side effects, such as dyspepsia, nausea, abdominal spasms, constipation, diarrhoea, concentration disturbance, headache, insomnia, peripheral neuropathy and rash can occur. Elevation of creatine kinase (CK) and liver tests can be seen, with or without symptoms. More serious side effects, mainly those of myopathy and liver toxicity are reported, though are rare. A recent meta-analysis of 18 trials including 71,108 persons, and 301,374 person-years of follow-up, concluded that treating 1000 patients with a statin would prevent 37 cardiovascular events, and 5 adverse events would be observed, including rhabdomyolysis. Atorvastatin was associated with the greatest risk of adverse events and fluvastatin with the least risk (31).

3.1. Myopathy

CK elevation occurs in one third of the patients with dyslipidemia, but this is often not related to intake of statins, since it's also seen in the placebo group (32). Elevations higher than 5 fold the upper limit of normal are not frequent.

Severe muscular problems such as myositis or rhabdomyolysis occur in 0.5% and 0.1% of the patients respectively (33), mostly in the first few weeks or months though theoretically they can occur **at** any time. Symptoms disappear a few days to four weeks after stopping statins (31,33,34). Other measures are not necessary, except in case of rhabdomyolysis (35).

The incidence of muscle disorders increases significantly in patients taking other medication besides a statin, such as cyclosporine or gemfibrozil (both inhibit the CYP 3A4 enzyme) (cfr. Table 3), but also niacin, macrolides, digoxin, antimycotics or warfarin. Rhabdomyolysis was also more common in case of renal failure, obstructive biliary disease or hypothy-

Table 3. — **Interaction with other medication**

	CYP 3A4	CYP 2C9
Induction	Barbiturates, carbamazepine, phenytoin, griseofulvin, nafcillin, rifampicin, primidone, fifabutin, troglitazone, St. John's wort	Barbiturates, carbamazepine, phenytoin, primidone, rifampicin
Inhibition	Clarithromycin, erythromycin, troleandomycin, fluconazole, itraconazole, ketoconazole, grapefruit juice, cyclosporin, tacrolimus, ritonavir, verapamil, mibefradil, nefazodone, fluoxetin	Amiodarone, cimetidine, trimethoprim-sulfamethoxazole, fluoxetine, fluvoxamine, isoniazide itraconazole, ketoconazole, metronidazole, sulfinpyrazone, ticlopidine, zafiruklast

roidism (33). In an overview of 475 hospitalized patients, it was found that multiple factors were present in 60 % of the cases (35).

The risk of developing myopathy is lowest with pravastatin or fluvastatin (31,36). This might be caused by a lower sensitivity of myocytes for these two statins, besides the fact that interaction with other medication is thought to be less common since these statins are minimally or not at all metabolized by the CYP3A4. Therefore pravastatin or fluvastatin should be preferred in case of the above mentioned associated pathology or in patients taking for example cyclosporin.

3.2. Liver toxicity

In 0.5% tot 3% of patients starting treatment with statins, an elevation of serum transaminases of minimum three times the upper limit of the normal concentration is seen. This elevation usually occurs within the first 3 months, is dose dependent, and is usually transient (37). The clinical importance is unclear (37-39). A recent study shows that patients with elevated transaminases are not at higher risk for statin hepatotoxicity when taking statins (40). Nevertheless, a few cases of liver cell necrosis and liver failure have been reported (41,42). Caution is thus necessary and it is best to stop the statin when transaminases continue to rise. An alternative statin can be tried out with careful monitoring.

There have been case reports suggesting that atorvastatin and also rosuvastatin may trigger autoimmune hepatitis in susceptible individuals (43,44). Nevertheless, considering the low frequency of significant adverse liver effects of statins, routine monitoring of liver function prior to or during therapy was said not to be indicated (37). However, when patients develop symptoms during therapy, the threshold to perform appropriate laboratory examinations should be low (43,44).

4. *Interactions of statins*

As mentioned before, atorvastatin and simvastatin are metabolised by the CYP 3A4 enzyme. Table 3 shows the different interactions. An augmented risk of developing myopathy is seen in combination with macrolides, azole derivates, viral protease inhibitors, fibrates,... all inhibiting these enzymes and thereby augmenting the blood concentration of statins. Potentialisation of the action of oral anticoagulantia and of digoxin by statins has been described.

5. *Indications for statins in liver diseases*

5.1. Non alcoholic fatty liver disease (NAFLD) : steatosis and steatohepatitis

The term NAFLD is used for a broad spectrum of liver diseases, from simple liver steatosis to steatohepatitis (NASH = Non Alcoholic Steatohepatitis) to liver fibrosis and cirrhosis. These diseases are difficult to become histologically differentiated from alcoholic liver damage nor from steatosis secondary to metabolic diseases or to certain medication. The aim of therapy is to avoid disease progression while still in the stage of steatosis or of beginning steatohepatitis. Treatment, first of all, consists of changing life style and diet. Besides that, researchers are looking for a more specific medical treatment. The use of fibrates, anti-oxidants and other agents is being studied, and some positive results already have been reported for gemfibrozil (45), metformin and glitazones (46-48).

The role of statins in NAFLD is uncertain. First of all, statins could be used in treating hyperlipidemia, a risk factor of NAFLD, but since mainly hypertriglyceridemia is present in NAFLD rather than hypercholesterolemia, fibrates could be preferred. A year of treatment with clofibrate did not show a significant improvement of liver tests or histology. Gemfibrozil does have proven effect, and this after only 4 weeks (45). This effect is not only due to decreased VLDL, but also because of decreased mobilisation of fatty acids from peripheral fat tissue. Secondly, metformin and glitazones, increasing the insulin sensitivity, induce a histological improvement of NASH (46-48). These findings confirm that insulin resistance is very important in the development of NASH and therefore represents the most important goal of treatment (46-48). Preliminary studies with atorvastatin (49,50) and pravastatin (51) result in an improvement of biochemical and histological parameters and are safe, but until now these studies concerned only very few patients (37).

5.2. Gall stone disease

Gall stones mainly consist of cholesterol, calcium bilirubinate, proteins and mucin. In Western countries 85% to 90% of the gall stones are cholesterol rich (52). Bile acid therapy with ursodeoxycholic acid and formerly with chenodeoxycholic acid is based on the knowledge that cholesterol is dissolved in bile acid rich and cholesterol-poor bile. Studies show that small size

non-calcified gall stones can be dissolved in a well functioning gall bladder (52).

The use of statins in gall stone therapy is controversial. Since a strong reduction of biliary cholesterol secretion is seen, a good effect can be expected in case of cholesterol rich gall stones, but the cholesterol saturation index does not seem to change, probably because a reduction of bile salts occurs simultaneously (53). Tazuma *et al.* showed that there is clearly more effect with the combination of simvastatin and ursodeoxycholic acid than with ursodeoxychol acid alone in multiple cholesterol gall stones, but this effect was not reported in case of solitary gall stones (54).

5.3. PBC and other cholestatic diseases (55-58)

Cholesterol subtypes

Hypercholesterolemia is one of the signs of chronic cholestatic liver disease because of the decreased biliary excretion of lipids, which can manifest itself clinically as xanthomas or xanthelasmata. The mechanism is different from that occurring in classical hypercholesterolemia, and it is generally accepted that patients with cholestatic liver disease don't have an increased risk to develop atherosclerosis. An increased HDL cholesterol and unusual, protective lipoprotein particles like lipoprotein X are seen (55-58). A large part of the exuberantly present LDL consists of this lipoprotein X, a lipoprotein, which is only seen in cholestatic liver diseases and which is rich in free (non-esterified) cholesterol and phospholipids. Indeed, the formation of cholesterol esters is low due to the decreased lecitin cholesterol acyl transferase (LCAT) activity. LPX seems to be protective against development of atherosclerosis (56-58). In addition, in chronic cholestasis, a low concentration of lipoprotein (a) is seen, and this also has a positive effect on the vessel wall, because of stimulation of cholesterol secretion from peripheral tissues (59).

The lipid profile however, can change during disease progression. In early PBC, HDL and apolipoprotein A1 (associated with HDL) are elevated, but they can decrease during the evolution to cirrhosis, despite a further reduction of bile secretion. Meanwhile, LDL and total cholesterol levels can increase (56-58). Serum triglyceride concentrations are normal most of the time.

Approach of hypercholesterolemia in PBC

Cholesterol concentrations in PBC can be decreased by the intake of medication. Ursodeoxycholic acid and statins both cause a decrease of cholesterol concentrations, though the effect of statins is more significant (59-61). Their use is safe but most often not really necessary (55,56,58). Remarkably, a decrease of alkaline phosphatase levels was seen in PBC patients treated with simvastatin (59). Recent data show that hypercholesterolemia, typically seen in chronic cholestasis, is not associated with an increased risk of cardiovascular disease. Consequently, according to the guidelines, no specific treatment aiming at the reduction of cardiovascular risk is necessary for hypercholesterolemia in PBC patients unless a low HDL-cholesterol or other compromising cardiovascular risk factors such as smoking or hypertension are present. These risk factors, defined by the National Cholesterol Education Program and other sources, are listed in Table 4 (1,56,57).

Re-evaluation of our patient

Since there seems to be a consensus in the literature about the cardiovascular risk not being elevated by hypercholesterolemia in PBC patients, we tried to find out what caused the cardiovascular problems in the above mentioned patient. Ultimately an increased lipoprotein (a) (720 mg/L) and a slightly increased

Table 4. — **Risk factors**

National Cholesterol Education Program :	**Others :**
• Age : men : > 45 years	– Serum Lp(a) concentration > 300 mg/L
women : postmenopausal	– homocysteïne concentration > 10 <mm>mol/L
• Hypertension (even under treatment)	– Familial cardiovascular history
• Smoking	– VLDL/TG-ratio > 0.3
• Diabetes mellitus	– High fibrinogen, factor VII or VIII conc,
• Small, dense LDL particles	high plasminogen-activator inhibitor
(men < 55 years, women < 65 years)	type 1 (associated with hyper TG),
• Serum HDL concentration < 35 mmol/dl	resistance to protein C inactivation or factor V or VIII
	– Insulin resistance (abdominal obesity) +/- hyperinsulinemia – High CRP concentrations – High leucocytosis and/or hematocrit – DD genotype for ACE – Chlamydia infection – Deficit of antioxidating vitamins – Arcus senilis, vascular bruits, absent pulsations in both lower limbs

hyperhomocysteinemia (16,2 µmol/L) were found, two factors increasing the cardiovascular risk, regardless of the fact that our patient has PBC. Folic acid and pyridoxine were added to her therapy, with normalisation of the plasma homocysteine concentration.

Conclusion

Patients with primary biliary cirrhosis do not have an increased cardiovascular risk due to hypercholesterolemia. Nevertheless the potential presence of other cardiovascular risk factors should always be kept in mind. Therefore it seems advisable to be cautious in every PBC patient developing cardiovascular problems and to look for underlying factors potentially causing an increased cardiovascular risk (Table 4). In such patients, adding a lipid lowering drug, such as a statin, might be necessary.

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