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Treatment of hypercholesterolaemia in patients with primary biliary cirrhosis may be more beneficial than indicated

Maria Luisa Balmer, Jean-François Dufour

Institute of Clinical Pharmacology, University of Berne, Berne, Switzerland

Summary

Cholesterol circulating levels are elevated in most of the patients with primary biliary cirrhosis. This review questions whether hypercholesterolaemia represents a cardiovascular risk in primary biliary cirrhosis and whether it should be treated. The published evidence indicates that hypercholesterolaemia in patients with primary biliary cirrhosis should be considered a cardiovascular risk factor only when other factors are present. Ursodeoxycholic acid the standard treatment of primary biliary cirrhosis improves the cholestasis and hereby lowers circulating levels of cholesterol. Primary biliary cirrhosis is not a contraindication to prescribe statins or fibrates to these patients. Interestingly, these two classes of drugs have been shown to improve not only the lipid profile but also the liver tests. In particular fibrates have been found to normalize liver tests in patients responding incompletely to ursodeoxycholic acid. Statins as well as fibrates possess specific anti-inflammatory properties which may be beneficial in primary biliary cirrhosis. In conclusion, hypercholesterolaemia in the absence of other cardiovascular risk factors does not require specific therapeutic intervention in patients with primary biliary cirrhosis. However, statins as well as fibrates seem to have beneficial effects on the primary biliary cirrhosis itself and deserve formal testing within clinical trials.

Key words: cardiovascular risk factors; cholestasis; cholesterol; statin; fibrate; primary biliary cirrhosis

Primary biliary cirrhosis is associated with cholestasis

The defect in biliary secretion in primary biliary cirrhosis (PBC) results in an elevated serum cholesterol level. Earlier studies found that 75–95% of patients with PBC have hypercholesterolaemia [1, 2]. Nowadays the disease is often diagnosed in the early stages and approx. one third of patients have hypercholesterolaemia [3]. In 1949, Ahrens and Kunkel published in the *Journal of Clinical Investigation* a now historic graph showing a positive correlation between the total bilirubin and lipid concentrations in the serum of patients with primary biliary cirrhosis [4]. Since then it has been recognised that patients with PBC have hypercholesterolaemia which, firstly, increases with cholestasis and, secondly, decreases with progression to end stage disease. In the intermediate stage the hypercholesterolaemia is characterised by increased LDL and HDL cholesterol levels. With disease progression there is a reduction in total cholesterol and in HDL cholesterol levels, suggesting that progressive reduction of hepatic cholesterol synthesis as well as impaired intestinal lipid absorption may overcome the cholestasis-related hypercholesterolaemia.

Is hypercholesterolaemia in PBC a cardiovascular risk factor?

In a classic study published in 1992, based on 312 patients followed at the Mayo Clinic for 7 years, the incidence of atherosclerotic death was 5%, not higher than in an age- and sex-matched control population [1]. However, this study relies for many cases on death certificates, a source of information which may not be accurate. Moreover, there was no information on the degree of atherosclerosis in these patients.

Two recent contributions from the Milan group help us to better judge the cardiovascular risk associated with hypercholesterolaemia in patients with PBC. In the first, Longo studied a cohort of 400 patients with primary biliary cirrhosis

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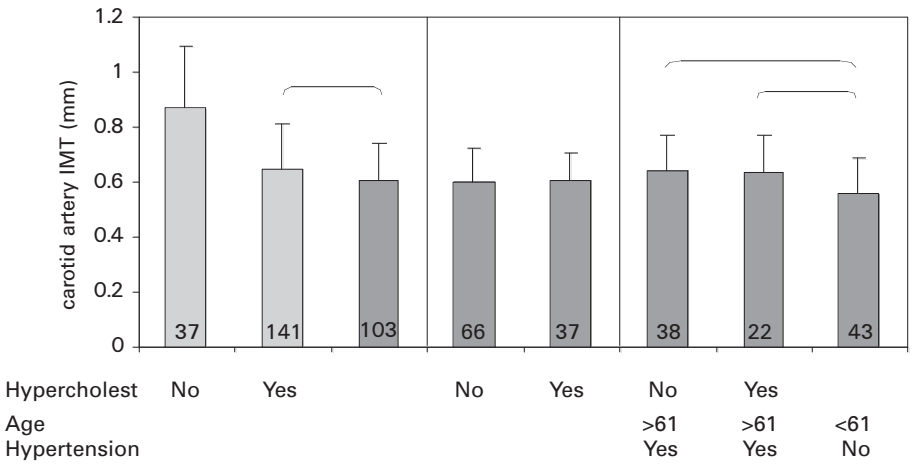
for 6.2 years [5]. Both fatal and non-fatal coronary and cerebrovascular events were considered and the hazard ratio was measured in patients with different categories of hypercholesterolaemia. Compared to patients with cholesterol below 5.2 mmol/L, who had a hazard ratio of 1, patients with serum cholesterol between 6.6 and 6.8 mmol/L had a hazard ratio of 3.9 with a p-value of 0.07. Interestingly, the patients with cholesterol above 7.8 had a lower hazard ratio of 2.4 with a p-value of 0.26, suggesting that extreme hypercholesterolaemia related to cholestasis is not atherogenic. This was actually also suggested in a recent publication where Su found that the lag time for LDL oxidation was significantly longer in patients with primary biliary cirrhosis compared to patients with hypercholesterolaemia alone [6]. The author speculates that this may be due to the presence of lipoprotein X in the serum of these patients. Lipoprotein X is a peculiar lipoprotein chiefly containing free cholesterol found in patients with cholestasis. In their study Longo et al. found that hypertension was significantly associated with cardiovascular events, with a hazard ratio of 3.8 and a p-value of 0.002. Diabetes had a hazard ratio of 4.8 with a p-value of only 0.06, probably due to the small number of patients (n = 15) with this associated cardiovascular risk factor.

What is the position with subclinical atherosclerosis? Nowadays it is possible to measure the intima-media thickness of the carotid artery by ultrasound imaging. Allocca and co-workers measured the intima-media thickness in 103 consecutive patients with primary biliary cirrhosis visiting their clinic. They compared their values with 141 control patients without hypercholesterolaemia and 37 patients with hypercholesterolaemia and no PBC (figure 1) [3]. Not surprisingly, the 37 patients with hypercholesterolaemia had a significantly greater intima-media thickness than the controls without hypercholesterolaemia. Interestingly, the patients with primary biliary cirrhosis had a significantly lower intima-media thickness than the control patients without hypercholesterolaemia. Breaking down the primary biliary cirrhosis patients between those with and those without hypercholesterolaemia did not change this result. However, taking other cardiovascular risk factors such as hypertension into account, it was found that the patients with PBC and without associated cardiovascular risk had a lower intima-media thickness than those with arterial hypertension or age above 61 years, independently of hypercholesterolaemia. Collectively, these results suggest that patients with hypercholesterolaemia and primary biliary cirrhosis need to be treated when they have an associated cardiovascular risk.

Figure 1

The intima-media thickness of 103 consecutive patients with primary biliary cirrhosis was significantly lower than that measured in 141 control patients without hypercholesterolaemia and 37 patients with hypercholesterolaemia and no PBC (left panel). Among the patients with PBC, there was no difference between the intima-media thickness of patients with hypercholesterolaemia and those without hypercholesterolaemia (middle panel). However, among the patients with PBC, those with hypertension and age above 61 years had greater intima-media thickness, independently of hypercholesterolaemia, than those aged under 61 years without hypertension (right panel).



Treatment with ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) reduces cholesterolaemia. In 1993 R. Poupon's group reported the effect of ursodeoxycholic acid on hypercholesterolaemia (figure 2) [2]. They studied 33 non-cirrhotic patients with primary biliary cirrhosis, 17 treated over 2 years with UDCA and 16 with placebo. At the end of the study period the total cholesterol was significantly lower compared with the value at entry in the group of patients taking ursodeoxycholic acid. There was also a significant reduction in LDL and VLDL cholesterol, but no effect on the phospholipid, total triglyceride and HDL concentrations. One year later, Lindor and co-workers confirmed these results: he showed that the reduction of serum cholesterol was greater in patients with a more marked reduction in serum bilirubin during the treatment and correlated with the basal choles-

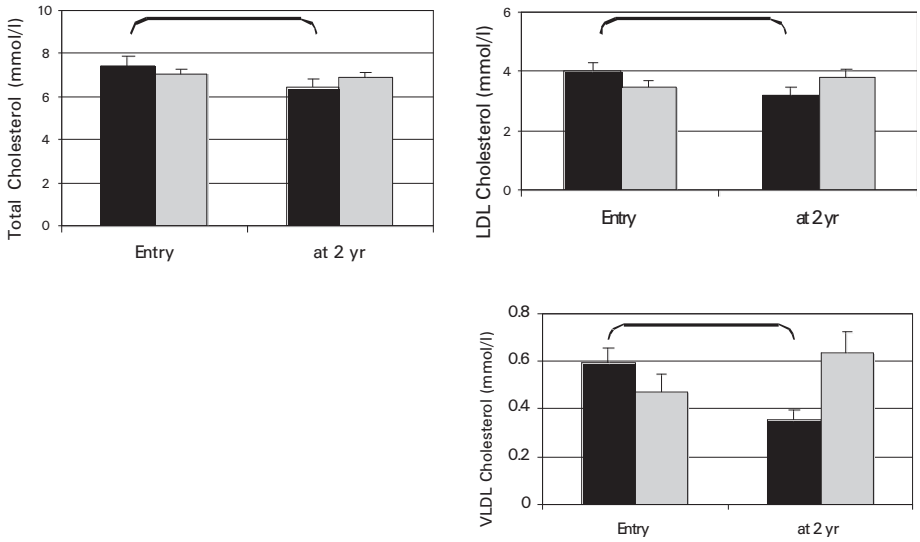


Figure 2

33 non-cirrhotic patients with PBC were randomised to be treated either with UDCA or placebo for 2 years. At the end of the study period total cholesterol was significantly lower compared to the value at entry in the group of 17 patients taking ursodeoxycholic acid. There was also a significant reduction in LDL and VLDL cholesterol.

terol level: the higher the basal cholesterol, the greater the effect of ursodeoxycholic acid [7]. Several mechanisms have been proposed to explain this hypocholesterolaemic effect of UDCA. Obviously, ursodeoxycholic acid improves cholestasis and cholesterol biliary excretion. It reduces the absorption of cholesterol from the gastrointestinal tract, and long-term treatment with ursodeoxycholic acid decreases the activity of the HMG-CoA reductase, the key enzyme in cholesterol synthesis. Also, UDCA increases the expression of LDL receptors on the hepatocytes and may also increase the conversion of cholesterol to bile acids.

Treatment with fibrates

A December 2007 literature search found 19 citations for articles dealing with primary biliary cirrhosis and bezafibrate. Of these 19 citations 18 were Japanese. The search found 5 citations (all Japanese) for fenofibrate and primary biliary cirrhosis. In a randomised study, Kurihara treated 12 patients with bezafibrate 200 mg twice daily and 12 patients with UDCA 600 mg per day [8]. Not surprisingly, the treatment with UDCA significantly improved ALT, alkaline phosphatase and g-GT levels. There were very modest effects on the total IgM concentration. Interestingly, bezafibrate improved all these parameters as well and the effects of the fibrate were significantly greater than the effect of UDCA (figure 3). What was to be expected from the addition of a fibrate to ursodeoxycholic acid in patients with an incomplete response to ursodeoxycholic acid? Nakai published a study in which 23 patients were randomised to either continue the treatment with ursodeoxycholic acid 600 mg/day (13 patients) or to additionally take bezafibrate 200 mg twice daily (10 patients) [9]. During the 12 months' duration of the treatment there was no change in the alka-

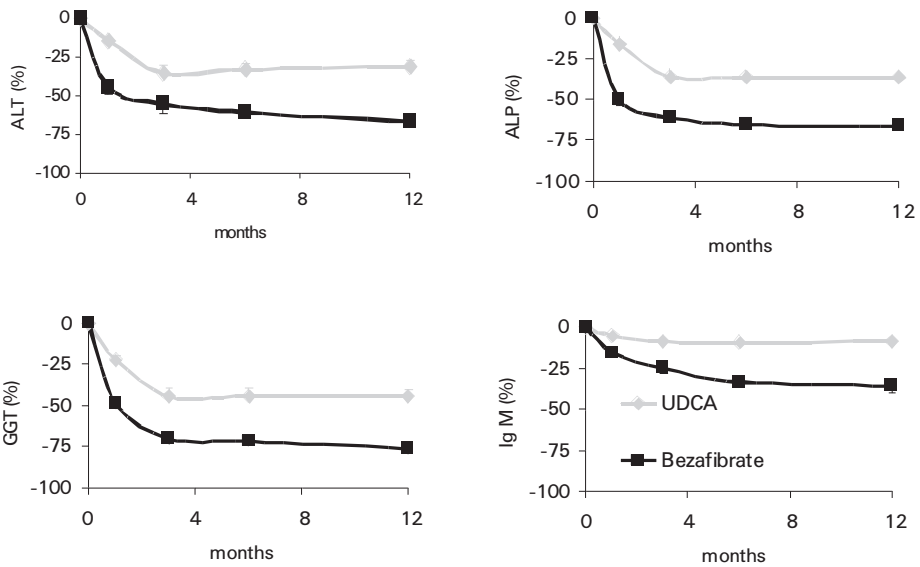


Figure 3

24 patients were randomised to receive either bezafibrate 200 mg twice daily or UDCA 600 mg/day. Not surprisingly, treatment with UDCA significantly improved ALT, alkaline phosphatase and the γ-GT levels (grey lines). There were very modest effects on the total IgM concentration. Bezafibrate improved all these parameters as well (black lines) and the effects of the fibrate were significantly greater than the effect of UDCA (adapted from [8]).

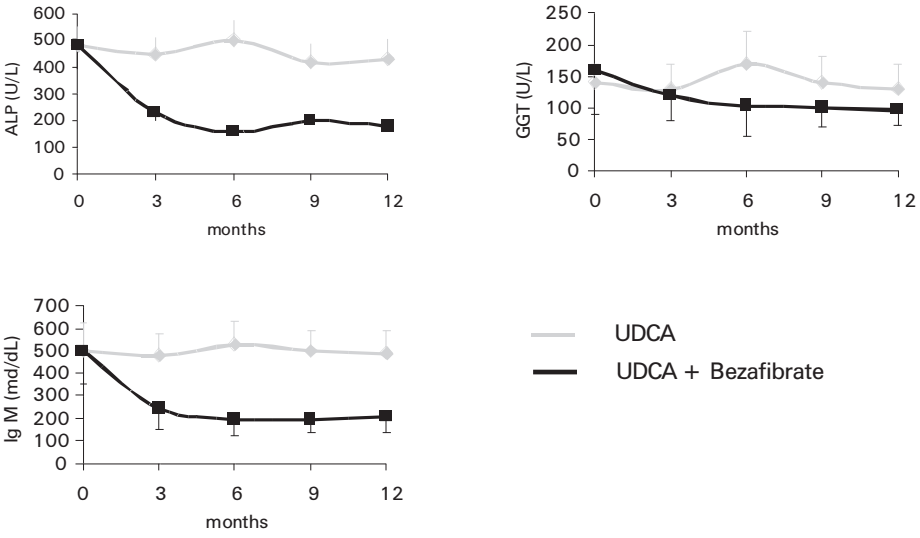


Figure 4

23 patients with an incomplete response to UDCA were randomised to either continue the treatment with UDCA 600 mg/day (13 patients) or to additionally take bezafibrate 200 mg twice daily (10 patients). During the 12 months' duration of the treatment there was no change in the alkaline phosphatase, g-GT and IgM levels in the patients continuing the treatment with ursodeoxycholic acid (grey lines), but there was a significant improvement in the patients additionally taking in bezafibrate (black lines). (adapted from [9]).

line phosphatase, γ-GT and IgM levels in the patients continuing the treatment with ursodeoxycholic acid, but there was a significant improvement in the patients additionally taking bezafibrate (figure 4). In these studies fibrates were well tolerated by patients with PBC. Remarkably, these studies did not report the effect of this treatment on the lipids, but it is known that experimentally fibrates stimulate the expression of MDR3 and the phospholipid flippase, leading to the production of a bile containing more phospholipids and less aggressive for biliary epithelial cells [10].

Nuclear hormone receptors, including peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), and the farnesoid X receptor (FXR), are transcription factors involved in the regulation of essential metabolic functions, including glucose and lipid metabolism, reverse cholesterol transport and the regulation of bile acids [25]. Fibrates are agonists for PPARα, activate Ω-oxydation, reduce the production of leucotrienes and have a negative effect on the production of interleukin-1, interleukin-6 and cyclooxygenase-2, as well as on the expression of ICAM1 and VCAM-1. Further, it has been shown that fibrates have beneficial effects on plaque thrombogenicity and plaque stability [24], and help to correct the lipid disorder associated with PBC. In total, fibrates appear to have a beneficial effect on patients with primary biliary cirrhosis, although the evidence is based on only a few small studies from Asian groups. Larger randomised controlled trials are needed to exclude type I and II errors and ensure the benefits for other populations as well.

Treatment with statins

With limited but encouraging results, Ramadori's group treated 6 patients with an incomplete response to UDCA with simvastatin 5–20 mg daily for 8 weeks [11]. The treatment was well tolerated and there was, as expected, a significant decrease in the total and LDL cholesterol levels. There was also a significant improvement in the alkaline phosphatase, the γ-GT and the IgM concentrations. In a more recent dose elevation study 15 patients were treated with atorvastatin [12]. These patients took 10 mg/day, 20 mg/day and 40 mg/day in 4-week consecutive periods. This was followed by a wash-out period of 8 weeks and a final follow-up visit at 20 weeks. In this study there was a significant improvement in cholesterol during the treatment period, but no effect on the γ-GT and the IgM concentration. Moreover, there was even an elevation of alkaline phosphatase levels. One patient in the 10 mg and 4 in the 40 mg period had to stop the treatment due to doubling of ALT levels. This raises the question of the safety of statins in patients with primary biliary cirrhosis. It is known that statins are safe in patients with elevated baseline liver enzymes [13] and in patients with chronic hepatitis C [14]. A study published by Marshall Kaplan in abstract form, based on his 10-year experience of more than 600 patients with primary biliary cirrhosis, found that in the 58 of these patients who took statins for a mean duration of 41 months, none had to stop the treatment because of side effects or worsening ALT levels (DDW 2007).

Moreover, statins have very interesting additional effects: they decrease the interferon-γ-induced MHC-2 protein expression on human endothelial cells and macrophages [15]. Statins have been shown to interact directly with LFA-1 and disrupt the interaction between LFA-1 and ICAM-1 [16]. It is also known from immunohistochemistry studies on biopsies of patients with primary biliary cirrhosis that induction of the expression of MHC-2 as well as of ICAM-1 on bil-

iary epithelial cells occurs, leading to infiltration of the portal tract with LFA-1 positive lymphocytes [17, 18]. There is an abundant literature on the suppressive effects of statins on inflammation, with reduction of C reactive protein [19, 20]. Statins also stimulate experimentally the expression of MDR3, resulting in the production of a less aggressive bile [21]. Since patients with PBC are at risk for osteoporosis, it is noteworthy that statins have osteogenic properties: they stimulate bone formation [22] and significantly reduce the risk of hip fractures [23].

Conclusion

Ursodeoxycholic acid is an established treatment for primary biliary cirrhosis: it has been shown to improve significantly transplantation-free survival in these patients. Nevertheless, some 50% of patients do not achieve a complete response, with persistent elevated alkaline phosphatase levels, and are at risk for disease progression. It is important to identify medications with which these patients could be treated. The literature shows that fibrates as well as statins could be prescribed to patients with PBC, not only to reduce hypercholesterolaemia but also to improve PBC. Simvastatin and bezafibrate are two medications which, specifically, deserve to be formally studied in larger randomised controlled trials.

Correspondence:
Jean-François Dufour
Institute of Clinical Pharmacology
University of Berne
Murtenstrasse 35
CH-3010 Berne
Switzerland
E-Mail: jf.dufour@ikp.unibe.ch

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