The use of ursodeoxycholic acid in patients with primary biliary cirrhosis : sense or nonsense

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Abstract

Ursodeoxycholic acid is the most widely evaluated drug for the treatment of primary biliary cirrhosis. The results of the first randomized controlled trials are very discordant in terms of survival benefit. This, however, can be explained by differences in methodology and insufficiently long period of treatment and follow-up. It has clearly been demonstrated that serum bilirubin levels and histological parameters such as piecemeal necrosis and fibrosis are validated predictors of prognosis in PBC. We re-analyzed the already published data using these parameters as surrogate endpoints. This analysis reveals that there is a significant positive effect of treatment of PBC with UDCA on serum bilirubin levels as well as on the progression of piecemeal necrosis and fibrosis. We therefore conclude that UDCA has a positive effect on the prognosis of PBC and can slow down the progression to end stage liver disease. (Acta gastroenterol. belg., **2003**, 66, **283-287**).

Key words : primary biliary cirrhosis, ursodeoxycholic acid.

Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by chronic destructive non-suppurative cholangitis of small and medium sized bile ducts resulting in loss of bile ducts, cholestasis and hepatocellular destruction, eventually leading to end stage liver disease.

The aetiology of primary biliary cirrhosis is unknown, but auto-immune mechanisms are likely to be involved. One mechanism might be the aberrant expression of MHC class I antigens on hepatocytes and bile duct cells that exposes them to immune mediated destruction by activated T-lymphocytes.

The drug that has been evaluated most widely to treat primary biliary cirrhosis is ursodeoxycholic acid (UDCA). Other treatments have been tested, but have been found to be either ineffective (e.g. colchicine, azathioprine) or to have too many important side-effects (e.g. corticosteroids, d-penicillamine, chlorambucil, cyclosporine, methotrexate).

Ursodeoxycholic acid is a bile acid that normally represents less than 5% of the total bile acid pool. Under treatment, however, this proportion can increase up tot 50% (1,2). The beneficial effects of ursodeoxycholic acid are attributed to three mechanisms (1,2). First there is a hepatoprotective effect resulting from the replacement of toxic hydrophobic bile acids by the more hydrophylic ursodeoxycholic acid and from the inhibition of solubilization of membrane bound phospholipids and cholesterol (that are both hepatotoxic). The second effect of ursodeoxycholic acid is the enhancement of choleresis with increased secretion of hydrophobic bile acids and phospholipids and reduction of the serum bilirubin levels. Finally ursodeoxycholic acid has an immunomodulatory effect by reducing the aberrant expression of MHC class I antigens on hepatocytes and bile duct cells and hence by diminishing the immune-mediated destruction by activated T-lymfocytes.

Literature review and analysis

Over the past ten years several clinical trials have been performed to evaluate the use of ursodeoxycholic acid in patients with primary biliary cirrhosis. The results of 11 of the first important double blind placebo controlled trials are briefly summarized in Table 1 (3-14). There were some other trials performed but we did not include them in our analysis because of either the small number of patients or because they were only published in abstract form.

At first view, the results of the selected trials seem sometimes very discordant, especially if we consider the results on survival. This makes it very difficult to clearly determine if there is a positive effect of the use of ursodeoxycholic acid on the natural evolution of primary biliary cirrhosis and whether it thus makes sense to use it systematically in PBC patients. In order to find an explanation for these discordant results we analyzed the study designs, the definition of end-points and the results of the trials.

The first problem we encountered comparing the different trials is that there is little uniformity in study design regarding the number of patients included, the dosage regimen, the duration of treatment and follow-up and the stage of PBC at entry. The trials we analyzed were double blind placebo controlled trials. The number of patients ranges from 18 (4) up to 548 (11). The UDCA dose was 13 to 15 mg/kg/day in most of the trials. In the trial performed by Battezzati *et al.* (7) only 500 mg (approximately 8,7 mg/kg/day) was given.

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Leuschner *et al.* (4) and Combes *et al.* (12) also used a lower dose of UDCA (10 – 12 mg/kg/day). Dosages lower then 13 to 15 mg/kg/day are now generally considered to be too low to have a substantial effect on disease outcome (3). Most authors opted for a treatment period of 2 years. Only Poupon *et al.* (6,11) and Lindor *et al.* (9) treated patients for 4 years or even 7 years (9), but the last two study years were always open label therapy. Some trials had an even shorter period of treatment : Leuschner *et al.* (4) only reached 9 months and Battezzati *et al.* (7) 6 to 12 months. Patient groups are mostly heterogenous in terms of stage of PBC at entry and stratification differs from one study to another.

A second problem is the definition of the end-points of the trials. In primary biliary cirrhosis 3 irreversible stages are identified (15) : a) the development of cirrhosis ; b) a terminal phase defined when serum bilirubin reaches 10 mg/dl (with or without the complications of cirrhosis) ; and c) death unless orthotopic liver transplantation (OLT) is performed. As hard end points of a trial evaluating the effect of UDCA on PBC we can thus consider death unless OLT as therapy failure and survival free of OLT as therapy succes. But the mean time to acquire cirrhosis from the early stages in untreated patients is 4 to 6 years (15) and the mean time for an untreated patient with cirrhosis to progress to end stage liver failure is approximately 4 years (15). From all the trials that were summarized only few had a treatment or even follow-up period that reached 4 years (6,9,11). Although some authors have claimed a positive effect of UDCA on survival, a clear-cut beneficial effect on this hard end-point has not undoubtly been demonstrated yet.

The same conclusion was made in the meta-analysis performed by Goulis *et al.* (16) and by the Cochrane Hepato-biliary Group the latter being up to now only published in abstract form (17). They also found that an insufficiently long period of treatment and follow-up and the differences in study design were responsible to a large extend for the inconclusive results regarding the effect of UDCA therapy . Heathcote (18) made the same remarks but she extracted the results from the trials that treated patients for 4 years or longer and ten came to the conclusion that UDCA does slow the progression of PBC. Nevertheless the discussion concerning the effect of UDCA on PBC remains open.

One way to cope with this problem would be to perform new double blind placebo controlled trials with a large numbers of patients that cover a longer period of therapy and follow-up. This, however, requires a complex organisation since large numbers of patients can only be included if multiple study centres are involved. The question would also rise if it is still ethical to give patients a placebo treatment when certain beneficial effects of UDCA have already been demonstrated. An alternative to new trials would be to review the available published data using parameters that are related to prognosis and that can predict survival or death without the necessity of a long period of follow-up for evaluation : the so-called surrogate end points.

Serum bilirubin levels

A first important parameter is the serum bilirubin level (SBL). Serum bilirubin is an independent predictive variable for bad prognosis in the natural evolution of primary biliary cirrhosis (19,20). It is known that if serum bilirubin reaches 10 mg/dl, survival is reduced to maximum 2 years. SBL is also an important determinant of the Mayo risk score, a well-validated predictor of survival in PBC (3). Bonnand *et al.* and van Hoogstraten *et al.* showed that bilirubin level in patients under treatment with UDCA should be interpreted as in untreated patients and keeps its prognostic value (20,21). Even more : normalization of the serum bilirubin level at 6 months of therapy indicates a good clinical outcome (20,21). According to Bonnand *et al.* (21) this leaves the possibility of identifying non-responders to UDCA in monotherapy.

As is obvious from Table 1, there was a statistically significant improvement of the serum bilirubin level except in the two trials in which the serum bilirubin level in the UDCA treated group was already normal at entry (4,14). In the Parès series, SBL in the placebo group increased significantly compared to the UDCA group. Only Lindor *et al.* (9) did not mention the results of UDCA on SBL. According to these results we may conclude that treatment of PBC with UDCA induces a significant improvement or prevents worsening of serum bilirubin levels and therefore has a positive effect on a very important factor of prognosis and hence on survival.

Histologic parameters

Another parameter we could use to evaluate the effect of UDCA on PBC is histology. We stated before that the development of cirrhosis is considered to be an irreversible phase in the natural history of primary biliary cirrhosis. Corpechot *et al.* even stated that we can use the onset of cirrhosis as an end point for trials (22). They also found that periseptal or periportal piecemeal necrosis is an independent prognostic factor for the development of cirrhosis. The progression of hepatic fibrosis is also an indicator of the evolution to cirrhosis.

There is again little uniformity in the study design of the trials concerning the evaluation of histological changes. Poupon *et al.* (6,11), Battezzati *et al.* (7) and Lindor *et al.* (9) did not evaluate histological parameters (Table 1).

Leuschner *et al.* (4) performed paired liver biopsies just before and just after treatment. Histological features (size of periportal field, connective tissue in periportal field, connective tissue spreading into the liver lobule, integrity of limiting plates, lymphocytes, plasma cells, polymorphonuclear cells, granulomas, bile duct inflammation and proliferation and proliferation of epithelial

Table 1. – **Results of initial placebo controlled trials of ursodeoxycholic acid in the treatment of primary biliary cirrhosis**

Auther (ref no)	Effect on serum bilirubin level	Effect on histology	Effect on pruritus / fatigue	Effect on survival	no patients	UDCA dose	Treatment / follow up
Leuschner *et al.*(4)	Normal at entry	Improved histologic stage : not significant More fibrosis in placebo : not significant	Improved, also in placebo	Not evaluated	18	10 mg/kg/day	9 mo / 3 mo
Poupon *et al.*(5)	Improved Significantly	Improved piecemeal necrosis significant Fibrosis not significant	Improved significantly	Not evaluated Improved Mayo risk score : significant	146	13-15 mg/kg/day	2 yr / -
Poupon *et al.*(6)	Improved Significantly	Not evaluated	Not evaluated	Improved significantly	145	13-15 mg/kg/day	2 yr-4 yr / -
Battezzati *et al.*(7)	Improved Significantly	Not evaluated	Improved significantly	Not evaluated	88	8,7 mg/kg/day	6 mo-12 mo / -
Lindor *et al.*(8)	Improved Significantly	Not improved Only histological stage evaluated	Not evaluated	Improved not significantly Improved Mayo risk score : significant	180	13-15 mg/kg/day	2 yr / -
Lindor *et al.*(9)	Not evaluated	Not evaluated	Not evaluated	Improved significantly	180	13-15 mg/kg/day	4-7 yr / -
Heathcote *et al.*(10)	Improved significantly	Improved Duct paucity : significant Hepatocellular ballooning : significant	Improved not significantly	Not improved	222	14/mg/kg/day	2 yr / -
Poupon *et al.*(11)	Improved significantly	Not evaluated	Not evaluated	Improved significantly	548	13-15 mg/kg/day	2 yr-4 yr / -
Combes *et al.*(12)	Improved significantly More fibrosis in placebo	More piecemeal necrosis in placebo	Less worsening significantly when SBL < or = 2 mg/dL	Improved significantly	151	10-12 mg/kg/day	2 yr / -
Vuoristo *et al.*(13)	Improved significantly	Improved Ductular proliferation : significant	Improved significantly	Not evaluated	90	12-15 mg/kg/day	2 yr / -
Parés *et al.*(14)	Normal at entry Increased under placebo	Improved Piecemeal necrosis : significant Histological stage significant	Improved significantly	Not improved	192	14-16 mg/kg/day	2 yr / -

cells) were all scored on a 0 – 4 scale of severity by several pathologists unaware of treatment status. Additional Giemsa-stained sections were evaluated for collagen content. Among UDCA patients the histological point score improved with a mean of 18%, especially in the integrity of limiting plates, the degree of bile duct inflammation and proliferation and the proliferation of epithelial cells. These differences were statistically not significant. Collagen content deteriorated in placebo treated patients, but this was also not statistically significant.

Poupon *et al.* (5) performed paired liver biopsies maximum 12 months before therapy and at the end of therapy. The following histologic features were graded : fibrosis, portal and periportal inflammation, piecemeal necrosis, ductular proliferation, parenchymal lobular necrosis, inflammation, cholestasis. The degree of bile-duct paucity was calculated as the number of bile ducts divided by the number of portal tracts. These separate values were used to calculate a liver-histology score The analysis showed a significant improvement of bile-duct paucity, ductular proliferation, portal mononuclear cell-infiltration, piecemeal necrosis, lobular inflammation, parenchymal necrosis, severity of cholestasis and the mean histological score. The severity of fibrosis did not differ significantly.

In the trial by Lindor *et al.* (8) liver biopsy specimens were compared sequentially using only histological staging following the criteria of Ludwig *et al.* There was no significant difference in histological stage, but more detailed analysis was not described in the article.

Heathcote *et al.* (10) evaluated histological changes in paired liver biopsies taken maximum 12 months before therapy and at the end of therapy. Histological staging for fibrosis and grading of lobular lymphoid inflammation, portal lymphoid inflammation, duct paucity, ductular proliferation and periportal (or paraseptal) hepatocellular ballooning were performed. There was significantly less progression of hepatocellular ballooning and duct paucity. There were no significant differences in the other parameters including fibrosis.

In the trial by Combes *et al.* (12) five pathologists evaluated paired liver biopsies simultaneously. They developed a scoring system for staging (stage I to IV) and for four parameters (piecemeal necrosis, portal inflammation, fibrosis and cholate injury). The average of the scores made by the five pathologists was used for statistical analysis. In patients with stage I and stage II disease there was a significant worsening of piecemeal necrosis in placebo treated patients. The average score also rose significantly in placebo treated patients. In stage III and stage IV disease with low SBL (SBL £ 2 mg/dl) there was less progression of fibrosis in UDCA treated patients. No differences were observed in stage III or stage IV with high SBL (> 2 mg/dl).

Vuoristo *et al.* (13) performed paired liver biopsies at the beginning and at the end of treatment. They scored the presence or absence of bile duct lesions, ductular proliferation, paucity of bile ducts, granulomas, piecemeal necrosis, fibrosis and complete nodules indicating cirrhosis. Severity of portal and periportal inflammation was scored from 0 to 3. A significant improvement was only seen in ductular proliferation.

Finally Parès *et al.* (14) compaired paired liver biopsies (maximum 6 months before therapy and at the end of a 2-year therapy) using staging according to the Ludwig criteria. Portal inflammation, piecemeal necrosis, lobular necrosis, ductular proliferation and cholestasis were also graded. Bile duct paucity was calculated as the number of bile ducts devided by the number of portal tracts. Histological stage and piecemeal necrosis were found to be significantly lower in patients treated with UDCA and the bile duct paucity was significantly higher in patients who were given placebo. Portal inflammation and lobular necrosis also decreased in patients taking UDCA.

Although the methodology is different from one study to another, some common findings can be noted.

Piecemeal necrosis is evaluated in 4 trials (5,12,13,14). Poupon *et al.* (5) and Parès *et al.* (14) showed a significant improvement of piecemeal necrosis. Combes *et al.* (12) found that UDCA treated patients in stage I or stage II disease did not show progression of piecemeal necrosis where as progression was present in placebo treated patients. Only Vuoristo *et al.* (13) could not demonstrate a positive effect of UDCA on piecemeal necrosis but detailed results of histological findings were not discussed in the article so a positive tendency of improvement cannot be evaluated. Periportal and periseptal piecemeal necrosis thus improved due to UDCA treatment in 3 out of 4 trials that evaluated this parameter. Since piecemeal necrosis is an independent prognostic factor of progression towards cirrhosis, the reported improvement by UDCA treatment may be seen as an indication of a true protective effect.

The progression of fibrosis was evaluated separately in 5 trials (4,5,10,12,13) apart from the histological stage that is of course also largely based on the presence of fibrosis and cirrhosis. Leuschner *et al.* (4) and Combes *et al.* (12) showed that in placebo treated patients there was significantly more fibrosis then in UDCA treated patients. Poupon *et al.* (5) found an improvement of fibrosis under UDCA although it was not statistically significant. Heathcote *et al.* (10) and Vuoristo *et al.* (13) did not find any difference between placebo and UDCA treated groups. In general there is a tendency towards protection against progression of fibrosis when evaluated. Treatment and follow-up period, however, are probably too short to mark a statistically significant difference.

Last but not least we have to mention that most trials show a beneficial effect of treatment with UDCA on clinical symptoms such as fatigue and pruritus (4,5,7,10, 12,13,14) and that no important complications or side-effects are reported.

Conclusion

The treatment of primary biliary cirrhosis with ursodeoxycholic acid remains controversial. Initial double blind placebo controlled trials showed discordant results on survival benefit. PBC however is a slowly progressive disease. We believe that the treatment and follow-up period of these trials were therefore too short to yield hard evidence of a beneficial effect on survival. Larger trials with a longer period of treatment and follow-up are needed. This, however, is not easy since it requires a multi-centre approach to collect a sufficient number of patients. Nevertheless, if we analyse the already published data by defining other end-points, a more clear and concordant result emerges.

Serum bilirubin level, an independent factor of bad prognosis in untreated patients as well as in patients treated with UDCA, improves significantly or remains normal under UDCA treatment in all trials, hence it is reasonable to accept a positive effect of UDCA treatment on prognosis. Histological parameters such as piecemeal necrosis and progression of fibrosis are indicators for the evolution to cirrhosis and the end-stage of PBC. Several of the reviewed trials show a clear improvement of these factors, especially of the piecemeal necrosis thus also indicating a positive effect of UDCA on disease progression. The effect of UDCA on the progression of fibrosis is less clear but we believe that here the treatment and follow-up period is most likely also too short to demonstrate a significant effect. Finally there is a positive effect on clinical symptoms such as pruritus and fatigue in the absence of important side-effects.

We may therefore conclude that ursodeoxycholic acid is a safe drug that improves the symptoms of the disease and that has a positive effect on certain parameters that are important predictors of disease progression.

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