

## Clinical audit

# Ursodeoxycholic acid therapy for primary biliary cirrhosis. A 10-year British single-centre population-based audit of efficacy and survival

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### Summary

**The effect of ursodeoxycholic acid treatment on survival in primary biliary cirrhosis was studied in 40 patients with symptomatic disease. Two patients developed early exacerbation of symptoms and stopped therapy in days; they are both alive 4 and 4½ years later. The other 38 patients have continued on treatment for up to 10 years. Results were compared with 12 other similar cases previously seen but not given specific therapy. Kaplan-Meier analysis showed that ursodeoxycholic acid treatment was associated with better survival ( $p < 0.05$ ) after the first two years of therapy. Predictors of favourable outcome included histological stage I disease. In 26 patients with primary biliary cirrhosis stage II, III or IV, therapy showed a trend to improved survival, but this was still significantly worse than the general population. Prognosis was not different between these different advanced stages. Symptoms improved in 28 out of 40 patients on ursodeoxycholic acid, but 50% had a recurrence by two years.**

**Keywords:** audit; ursodeoxycholic acid; biliary cirrhosis

Primary biliary cirrhosis can only be cured by liver transplantation, and even then recurrences have been reported.<sup>1</sup> Several specific drug treatments have been tested but these are, in general, toxic and ineffective. When bile acid therapy was first found to be useful in chronic liver disease it was tried in primary biliary cirrhosis and a pilot study gave encouraging results.<sup>2</sup> Symptoms improved, and serum biochemistry was normalised. It was therefore decided to offer all local symptomatic patients with primary biliary cirrhosis treatment with ursodeoxycholic acid (UDCA). As attempts to join multicentre studies were unsuccessful, this was conducted as a single-centre study from June 1987.

### Patients

All patients with symptomatic primary biliary cirrhosis from the local resident population of 153 000 were considered for treatment after liver biopsy.<sup>3</sup> Since 1987, 40 patients have been

seen and all accepted treatment. Results were compared with those from 12 patients previously diagnosed and not given specific treatment.

The patients were mostly women (three were men) and the age at entry into the study ranged from 32–86 years, median 67 years. All patients had some specific symptom (lethargy, pruritus, abdominal pain, diarrhoea) or complication (jaundice, gastro-intestinal haemorrhage, ascites, encephalopathy) which were related to their liver disease. Neither lethargy nor musculoskeletal disease were considered specific symptoms: all patients with these complaints had at least one other symptom. In addition to symptoms, they all had at least two out of three of the following:

- positive serum mitochondrial antibody (36 patients)
- positive liver histology (38 patients; two unsafe to biopsy)
- typical serum biochemistry with raised glutamyl transferase and alkaline phosphatase (39 patients).

### Treatment

Initially all patients were given UDCA at a daily dose of 750 mg ( $3 \times 250$  mg capsules). There was evidence that this would induce the maximal shift in the bile acid pool to enrich the natural UDCA content of 2% to about 50%.<sup>4</sup> A trial of 1000 mg daily produced some additional serum biochemical improvement. However, this was not significant except for bilirubin and IgM levels, and even this was not sustained at 2 years, so this dose was not continued. No attempt was made to titrate dose according to weight or any other variable. The average daily dose per kg bodyweight on 750 mg daily was 13 mg/kg, divided as convenient.

### Follow-up

Patients were asked to attend for review at least four times in the first year (after 1, 3, 6, and 12 months) and the earlier cases were also seen at 2, 4, and 9 months. Thereafter they were seen 6-monthly. They were questioned about symptoms and weighed. All patients were seen by a single consultant gastroenterologist. At every visit, blood was sent for liver function tests, immunoglobulins, full blood count, prothrombin time, cholesterol, calcium, glucose,

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electrolytes and creatinine. Serum UDCA levels were measured by radioimmunoassay as a test of compliance in 14 patients. Eight patients had repeat liver biopsy after 4 months of therapy to assess progress. Triolein breath tests were performed before and after 4 months treatment in 11 patients to assess any effect on steatorrhoea.

During the period of the study, liver transplantation became more freely available and a transplant service started in Newcastle. Referrals for liver transplant were based on clinical condition, bilirubin level, histological grade and patient preference. Three patients were referred for surgery. None has been transplanted to date, so a true life table analysis was possible.

**Results**

**SYMPTOMS**

These were reported to improve in 28 patients on ursodeoxycholic acid therapy, but had returned in half of these by two years; two had exacerbation of symptoms which led to cessation of treatment. The rest reported no change.

**BIOCHEMISTRY**

Exact calculation was difficult over the duration of the study as laboratory methods and ranges changed. A general observation was prompt reduction of elevated glutamyl transpeptidase and alkaline phosphatase levels, and to a lesser extent of alanine transaminase level. This was maximal at 4–6 months, and after a plateau there was a slight rise in value after 2 years, but not overall to original values. Bilirubin and mitochondrial antibody titres showed no consistent change on UDCA therapy. The average initial triolein breath result was at the borderline of normal and abnormal (0.38% dose/mmol CO<sub>2</sub>/kg) and did not change on therapy (0.42% dose) indicating no effect on steatorrhoea. UDCA levels were 0.05–1 μmol/l before treatment and 4–235 μmol/l (median 25) after treatment in 14 patients, indicating good compliance.

**Table 1** Comparison of treatment groups

	No UDCA treatment	UDCA treatment
Number of patients	12	40
Median age years	59	67
Histological stage I	3	13
Histological stage II–IV	8	26
No biopsy possible	1	1

**HISTOLOGY**

Four patients with histological stage I disease and four with stage III disease had biopsies immediately before starting treatment and at 4 months. Two of these had improved with reduction of inflammatory tissue and another one had reverted to completely normal.

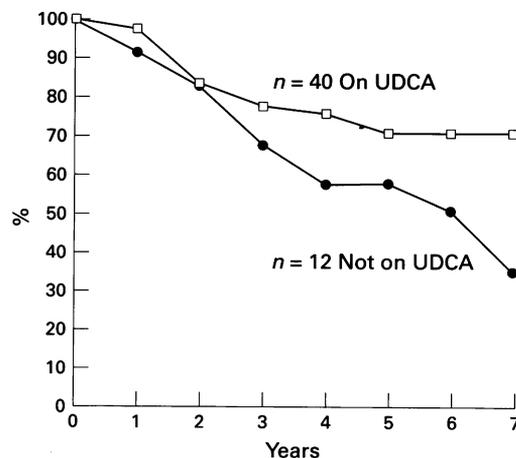
**SURVIVAL**

Forty patients who started on UDCA therapy were followed for up to 10 years, and compared with the 12 on no therapy (table 1) and the published literature prior to UDCA therapy being used. Life tables were constructed using the Kaplan-Meier technique. Comparison was made with the general population using the 1991 census standardised for age, sex, and the North East population. Differences were calculated by confidence intervals. After the first 2 years there was a definite survival advantage for the UDCA-treated patients (p <0.05) (figure). This tended to increase with time. At 7 years the survival rates were 71 vs 35% for the treated and untreated patients, respectively. Even on UDCA therapy, survival was less than the general population (p <0.05). Predictors of survival (measured before UDCA therapy started) were lower age, lower serum bilirubin, lower serum IgG (p <0.01); higher haemoglobin, higher serum albumin, and histological stage I (p <0.05).

The 22 deaths in the 52 patients were mainly related to liver disease, including upper gastrointestinal bleeding, liver failure, spontaneous bacterial peritonitis and hepatoma. Three patients died of infective lung disease, three of ischaemic heart disease and two of cerebrovascular accident. Median follow-up in the patients on no therapy was 18 months compared with 30 months in the patients on UDCA.

*Histological stage I disease*

Although the median age was the same (67 years), survival in patients with histological stage I disease was noticeably better than in those with more advanced disease. The 13 patients with histological stage I disease allocated to UDCA therapy were followed for 1–9.5 years, (median 4). One patient stopped treatment for early exacerbation of symptoms and is still alive 4 years later. Another patient, aged 74 years, stopped treatment at 4 months because of difficulty attending clinic and lack of improvement of skeletal symptoms; she died at 1 year of pneumonia. One patient, aged 65 years, continued on treatment for 7.5 years and then stopped; she was a heavy drinker and died at 9.5 years of a stroke.



**Figure** Survival of patients with primary biliary cirrhosis

**Table 2** Case report: a 74-year-old woman with stage I primary biliary cirrhosis, treated with continuous UDCA

	At start	1mth	4 mths	1 year	8 years
Bilirubin ( $\mu\text{mol/l}$ )	10	8	17	19	10
Alkaline phosphatase (IU/l)	134	70	50	59	79
$\gamma$ -Glutamyl tranpeptidase (IU/l)	220	84	32	40	36
IgM (g/l)	7.68	2.95	2.46	2.80	2.87
Symptoms	lethargy/pruritus	better	cured		absent
Liver biopsy	stage I		normal		
Mitochondrial antibody titre	160			40	40(M2+)

None of the patients with histological stage I disease who continued on treatment died. When the whole group of 13 were analysed by strict intention-to-treat analysis, survival was the same as the general population. One patient, a woman aged 74 years at entry, had reversion to normal histology, loss of pruritus and lethargy, and complete biochemical normalisation by 4 months. Her mitochondrial antibody titre fell from 160 to 40. She has been followed up for 8 years on bile acid therapy and remains well with normal laboratory results, apart from a mitochondrial antibody titre of 40 and positive M2 antibody, and may be regarded as a complete cure (table 2).

#### Histological stage II–IV disease

No differences between outcome in these different stages could be identified. However, the numbers were small, particularly in histological group II. Survival was apparently better than in untreated patients but this did not achieve statistical significance. Patients had a significantly worse survival than the general population ( $p < 0.01$ ).

Three patients agreed to referral for liver transplantation. One was a man of 48 years who had ischaemic heart disease and histological stage III disease, and he died of a myocardial infarction. One was a woman of 73 years with histological stage IV disease in liver failure at the time of diagnosis who felt she was unsuitable for surgery. One other woman, aged 59 years, who had histological stage III disease is waiting for transplant. Since no transplants have yet been performed, survival tables are a true life and death analysis.

#### Discussion

Bile acid therapy was initially felt to be contraindicated in liver disease and indeed this was stated in the British National Formulary until recently. This was clearly inappropriate. As early as 1980, Leuschner's group in Frankfurt reported improvement in chronic hepatitis during chenodeoxycholic acid treatment for gallstones. Work was inhibited, however, until

#### Summary points

- ursodeoxycholic acid therapy improves survival in symptomatic primary biliary cirrhosis, and normalises it in histological stage I disease.
- there is also biochemical and symptomatic improvement

the publication of an uncontrolled trial of 15 primary biliary cirrhosis patients treated with UDCA with encouraging results.<sup>2</sup> Increasingly wide use of UDCA followed and patients with primary biliary cirrhosis now usually receive this therapy.

There is no long-term randomised prospective placebo-controlled trial which proves disease modification and improved survival, nor is there ever likely to be. Three large studies in France, Canada and the US, which were placebo-controlled for 2 years, followed by 2 years open treatment, all indicated that UDCA reduces or delays the need for liver transplant.<sup>5–7</sup> Transplant-free survival was improved on meta-analysis.<sup>8</sup> The natural history of even asymptomatic primary biliary cirrhosis is not benign,<sup>9–12</sup> and even stage I disease regularly and rapidly progresses to later stages.<sup>13</sup>

The present work was carried out in a single centre, and is the only British survival study to be published. It is population-based, and probably included almost all of the local symptomatic cases of primary biliary cirrhosis during the study period. The dose of UDCA is arbitrary, but previous studies in gallstone disease showed that 750 mg daily had a maximal effect on enrichment of the bile acid pool.<sup>4</sup> Studies on serum and biliary bile acids suggest that this is also likely to be the case in primary biliary cirrhosis.<sup>14–17</sup> It is not possible to induce more than about 50% conversion of the bile acid pool of UDCA despite further increasing doses. By contrast, for Caucasians at least, a standard dose of only 500 mg daily is probably inadequate.<sup>18</sup>

The mechanism of action of UDCA may be immunomodulatory in part, but probably of more importance is prevention of progressive cholestatic liver damage following the initial immunological insult. UDCA is a hepatoprotective bile acid which counteracts the effects of retention of chenodeoxycholic acid and cholic acid.<sup>19</sup> UDCA therapy currently costs £1.73 daily, but may be an economy if it avoids or defers the need for liver transplant in some patients. In addition, it may replace requirement for other treatments. The case may be made for treatment of all symptomatic cases of primary biliary cirrhosis not actually transplanted or terminally ill.<sup>20</sup> There could even be a role in asymptomatic disease.

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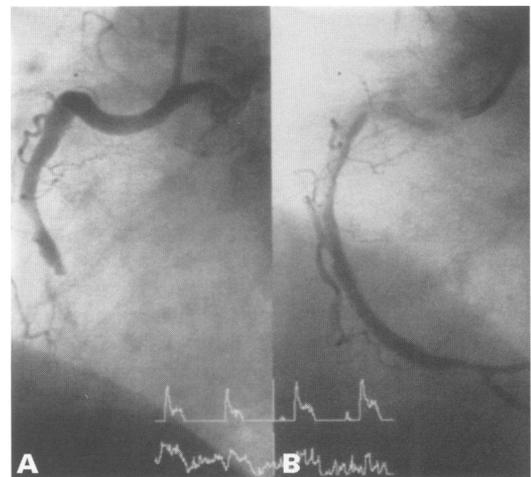
## Images in clinical medicine

### Intravascular monitoring of successful reperfusion following rescue angioplasty

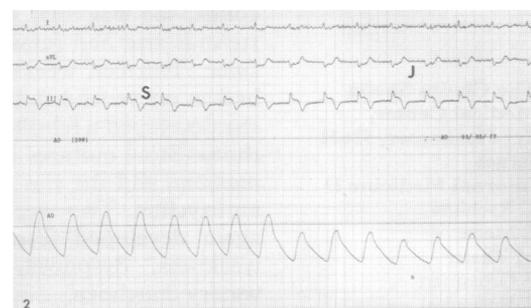
A 70-year-old woman underwent rescue angioplasty to the right coronary artery following failed thrombolysis (figure 1A). Ischaemic pain and electrocardiographic (ECG) changes resolved when distal vessel patency had been achieved (figure 1B). Five minutes after successful reperfusion, the intra-arterial pressure dropped, without any evidence of vessel occlusion. These changes were episodic and unrelated to respiration. Simultaneous pressure tracings and ECGs showed an intermittent junctional rhythm which coincided with the fall in blood pressure (figure 2). This figure demonstrates two points. Firstly, the important contribution of atrial systole to cardiac output is demonstrated by the fact that sinus beats were accompanied by a 20-30 mmHg rise in blood pressure compared with junctional beats. Secondly, this case also demonstrates that hypotension during alternative reperfusion strategies such as thrombolysis, may be a marker of success rather than an unfavourable reaction to the strategy used.

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**Figure 1** (A) Occluded right coronary artery; (B) patent right coronary artery after percutaneous transluminal coronary angioplasty and stent



**Figure 2** Aortic pressure: S, sinus beats; J, junctional beats