Cost effectiveness of using ursodeoxycholic acid to treat primary biliary cholangitis

ABSTRACT

Primary biliary cholangitis is a chronic inflammatory, autoimmune cholestatic liver disease, which untreated will usually progress to end-stage biliary cirrhosis. The aims of treatment and management of primary biliary cholangitis are the amelioration of associated symptoms, particularly pruritis and fatigue, and the prevention of end-stage liver disease. The presentation, natural history and clinical course are variable. Recent published European and UK clinical guidelines have emphasized the need for risk stratification and an individualized approach to patient management in primary biliary cholangitis. The bile acid, ursodeoxycholic acid, is established as the first-line treatment of primary biliary cholangitis. Assessment of clinical response to treatment is based on specified improvements in serum liver tests including near normalization of the serum alkaline phosphatase level at 1 year. At least two thirds of patients with primary biliary cholangitis should respond to ursodeoxycholic acid after 1 year's treatment. The correct dosage of ursodeoxycholic acid is determined by body weight viz 13–15 mg/kg/day. A significant number of patients with primary biliary cholangitis in the UK are being underdosed. Over a third of ursodeoxycholic acid partial responders become responders within 2 years after increasing the ursodeoxycholic acid doses to recommended levels. While transplant rates for primary biliary cholangitis have halved over the last 20 years, it is clear that optimizing the dose of ursodeoxycholic acid in partial responders would further decrease morbidity, mortality and the need for liver transplantation.

Primary biliary cholangitis, previously known as primary biliary cirrhosis, is a chronic, autoimmune, progressive cholestatic liver disease which is characterized by inflammation and selective destruction of small and intermediate intrahepatic bile ducts (Beuers et al, 2015a). It usually leads to cholestasis, liver fibrosis and eventually cirrhosis and liver failure (Selmi et al, 2011).

In keeping with other autoimmune diseases, there is a strong female predominance with a female to male ratio of about 9:1. The majority of patients present in middle age in their 40s or 50s. However, an increasing number of women with primary biliary cholangitis are being diagnosed in their early 30s, which is associated with a worse long-term prognosis (Selmi et al, 2011).

The pathogenesis of primary biliary cholangitis, in common with other autoimmune diseases, is complex and multifactorial. It involves a series of events including complex immunopathological alterations causing injury to small and intermediate bile ducts, perpetuated by the toxic effects of cholestasis and hydrophobic bile acids, leading to bile duct loss, fibrosis and cirrhosis (Hirschfield and Gershwin, 2013).

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Patients with primary biliary cholangitis may present with fatigue, pruritus and, rarely, with late stage disease, namely jaundice and liver failure. However, most patients are asymptomatic at the time of diagnosis. Patients with primary biliary cholangitis are often identified by routine blood tests indicating cholestasis, i.e. elevated serum levels of alkaline phosphatase and gamma glutamyltransferase. Serum levels of aminotransferases (alanine transferase, aspartate transaminase) and occasionally bilirubin may also be increased.

At present, according to the latest recently published European Association for the Study of the Liver and British Society of Gastroenterology clinical practice guidelines (Hirschfield et al, 2017, 2018), the diagnosis of primary biliary cholangitis is established by the presence of elevated serum markers of cholestasis (alkaline phosphatase, gamma glutamyltransferase) and antimitochondrial antibodies (antibody titre ≥1:40). Antimitochondrial antibodies are detected in more than 90% of patients with primary biliary cholangitis and their specificity in primary biliary cholangitis is greater than 95% (Hirschfield et al, 2017, 2018). Although a liver biopsy can identify non-suppurative cholangitis, interlobular bile duct damage and the stage of fibrosis, this procedure is no longer considered necessary to confirm the diagnosis of primary biliary cholangitis (Hirschfield et al, 2017, 2018).

Ursodeoxycholic acid: mode of action in cholestasis

The naturally occurring bile acid, ursodeoxycholic acid, at a dosage of 13–15 mg/kg/day, has become established over the past 20 years as the first-line treatment for patients with primary biliary cholangitis. European Association for the Study of the Liver guidelines recommend that patients with primary biliary cholangitis should be treated with ursodeoxycholic acid for life, maintained at this dose (Hirschfield et al, 2017). Ursodeoxycholic acid is more hydrophilic than other more potentially toxic hydrophobic bile acids, such as chenodeoxycholic and deoxycholic acids (Beuers et al, 2015b; Trauner et al, 2017). Normally, ursodeoxycholic acid makes up approximately only 1–4% of the bile acid pool in human bile. However, after regular oral administration it becomes the predominant bile acid, and the degree of biliary enrichment with ursodeoxycholic acid directly correlates with the improvement in serum liver tests (Beuers et al, 2015b; Trauner et al, 2017).

Table 1 Biochemical criteria used to assess optimal response to ursodeoxycholic acid in primary biliary cholangitis

Study centre (reference)	Evaluation/ assessment time	Biochemical suboptimal response to ursodeoxycholic acid
Rochester (Jorgensen et al, 2002)	6 months	Alkaline phosphatase >2 x upper limit of normal range or Mayo score >4.5
Barcelona (Parés et al, 2006)	1 year	Alkaline phosphatase >1 x upper limit of normal range and decrease in alkaline phosphatase <40%
Paris 1 (Corpechot et al, 2008)	1 year	Alkaline phosphatase >3 x upper limit of normal range or aspartate aminotransferase >2 x upper limit of normal range or bilirubin >1 mg/dl
Rotterdam (Kuiper et al, 2009)	1 year	Abnormal bilirubin and/or albumin levels
Toronto (Kumagi et al, 2010)	2 years	Alkaline phosphatase >1.67 x upper limit of normal range
Paris 2 (Corpechot et al, 2011)	1 year	Alkaline phosphatase>1.5 x upper limit of normal range or aspartate aminotransferase >1.5 x upper limit of normal range or bilirubin >1 mg/dl

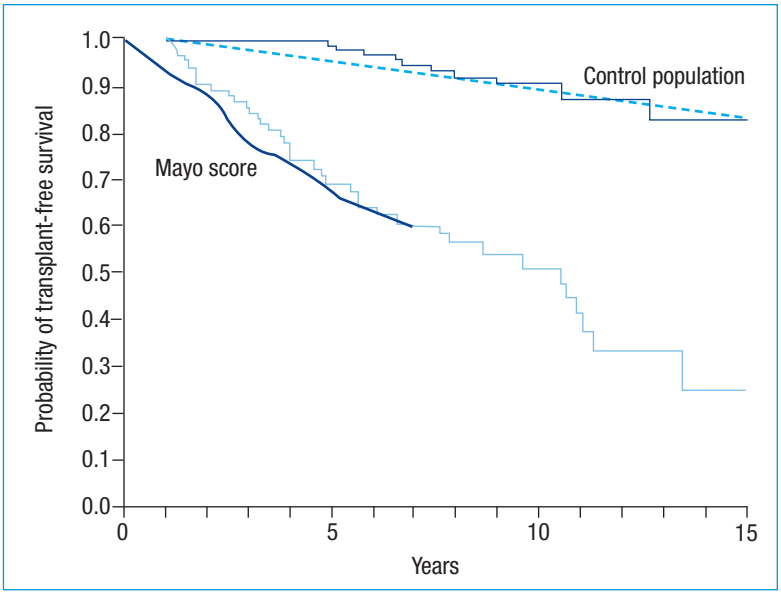

Figure 1. Biochemical response to ursodeoxycholic acid and relationship to long-term prognosis in primary biliary cholangitis. From Corpechot et al (2008).

Ursodeoxycholic acid has a number of potentially beneficial actions in cholestasis. First, it has a choleretic action increasing the impaired biliary flow in hepatocytes and cholangiocytes and stimulates the membrane targeting and insertion of transport proteins (Beuers et al, 2015b; Trauner et al, 2017). Second, ursodeoxycholic acid also exerts cytoprotective (e.g. anti-apoptotic) effects in hepatocytes and cholangiocytes against bile salt-induced apoptosis (Beuers et al, 2015b; Trauner et al, 2017). Third, ursodeoxycholic acid reduces the hydrophobicity of bile rendering it less toxic to the biliary tree (Beuers et al, 2015b; Trauner et al, 2017). Last, ursodeoxycholic acid strengthens the 'biliary bicarbonate umbrella'. Biliary bicarbonate is thought to protect hepatocytes and cholangiocytes against the toxic effects of bile acids (Beuers et al, 2010).

Dose-ranging studies have shown that the optimal dose of ursodeoxycholic acid in patients with primary biliary cholangitis is 13–15 mg/kg per day. This dose is superior to 5–7 mg/kg/day or 23–25 mg/kg/day. In patients with primary biliary cholangitis, ursodeoxycholic acid significantly reduces levels of serum alkaline phosphatase, gamma glutamyltransferase, bilirubin, cholesterol and immunoglobulin M (IgM), and improves liver histology.

Ursodeoxycholic acid can be administered as a single oral daily dose or divided doses; anecdotally some patients tolerate liquid preparations better. It is very safe, with a low prevalence of minimal side effects when administered to patients at its recommended dose (weight gain of up to 3 kg in the first year, hair thinning, and, rarely, flatulence and diarrhoea) (Hirschfield et al, 2017).

Biochemical criteria for optimal response to treatment with ursodeoxycholic acid

Reports from different centres around the world (Jorgensen et al, 2002; Parés et al, 2006; Corpechot et al, 2008, 2011; Kuiper et al, 2009; Kumagi et al, 2010; Harms et al, 2018) have confirmed that the biochemical response to ursodeoxycholic acid accurately predicts the long-term outcome and survival in patients with primary biliary cholangitis as indicated by improvement of one or more biochemical tests, when assessed at 1 year (*Table 1*). The long-term survival of the 60–70% of patients with primary biliary cholangitis who respond to ursodeoxycholic acid at 1 year is similar to that estimated for a matched control population (Harms et al, 2018) (*Figure 1*). In marked contrast partial responders have an increased morbidity from decompensated cirrhosis, an increased mortality and an increased risk of requiring liver transplantation.

Several definitions of optimal biochemical response to ursodeoxycholic acid have been proposed (*Table 1*), and approximately 30–40% of patients fulfil at least one condition of incomplete biochemical response (Jorgensen et al, 2002; Parés et al, 2006; Corpechot and Poupon, 2007; Corpechot et al, 2008, 2011; Kuiper et al, 2009; Kumagi et al, 2010; Harms et al, 2018). These patients, classified as partial responders, have an increased risk of progression events, and decreased survival time free of transplantation. In a recent study from the Global PBC Study Group, the incidence of major hepatic complications was assessed in 3224 patients with primary biliary cholangitis treated with ursodeoxycholic acid from 16 European and north American countries (Harms et al, 2018). The group was studied after a median follow up of 8 years. In this large international cohort, up to 15% of ursodeoxycholic acid-treated patients with primary biliary cholangitis developed major non-neoplastic, cirrhosis-associated hepatic complications

within 15 years. Patients with a biochemical partial response after 12 months of ursodeoxycholic acid had a 10-year complication rate of 37.4%, compared to only 3.2% in biochemical responders (Harms et al, 2018). Biochemical partial response to ursodeoxycholic acid was an independent risk factor for these complications. Therefore, patients with a suboptimal biochemical response to ursodeoxycholic acid require further treatment with combination therapy of ursodeoxycholic acid and a second-line agent such as obetocholic acid or fibrates (Hirschfield et al, 2017).

Importance of correct dosing with ursodeoxycholic acid

From the data discussed above, it is clear that it is essential to ensure that an individual patient with primary biliary cholangitis is given the correct dose of ursodeoxycholic acid in order to maximize the chance of achieving a complete biochemical response and a normal life span. There is evidence to suggest that underdosing with ursodeoxycholic acid may be especially prevalent in the UK compared with other European countries. The UK experience appears to differ from that of other European countries. Corpechot and Poupon (2007) reported that French, German, Spanish and Greek observational studies had consistently found that long-term treatment with ursodeoxycholic acid improved survival free of liver transplantation in comparison with the predicted survival of untreated patients. However, no such effect was observed in the UK series. They suggested that ursodeoxycholic acid in the UK may have been preferentially prescribed to patients with more rapidly advancing disease, as suggested by Prince et al (2002) in an earlier study from the north east of England of 770 patients with primary biliary cholangitis. It is important to note that in this group the median daily dose of ursodeoxycholic acid received in between 1987 and 2000 was 7.5 mg/kg, only half of the recommended therapeutic dose.

A more recent unpublished UK survey of 600 patients from the PBC Foundation in 2014 found that the mean daily dose was only 8.4 mg/kg/day. In addition, some UK audits have suggested that the proportion of underdosed patients is probably higher in district general hospitals but also occurs in specialist hepatology units.

In a study of 851 Dutch patients with primary biliary cholangitis diagnosed between 1988 and 2012, patient management was assessed in relation to liver test results during ursodeoxycholic acid treatment (Lammers et al, 2006). Biochemical response at 1 year was analysed retrospectively according to Paris 1 criteria. They confirmed that transplant-free survival of partial responders (60%) was significantly worse than that of responders (87%). Management was modified in 46/157 (29%) partial responders – most frequently (in 26/46 patients) an increase in ursodeoxycholic acid dosage. Subsequently, 9/26 (35%) partial responders became responders within the next 2 years. No trend towards more frequent changes in management over time was seen. The authors concluded that the observation that response-guided management did not increase over time 'suggests that awareness of the concept of biochemical response requires further attention' (Lammers et al, 2006, 2014).

In a paper from the UK-PBC group (Carbone et al, 2016), data from 1916 UK patients with primary biliary cholangitis showed that the median dose of ursodeoxycholic acid was 12 mg/kg, implying that 50% of patients were receiving less than the recommended dose and were thus underdosed. As expected the great majority of adequately treated patients achieved a complete response using the Paris 1 criteria in contrast to patients who were being underdosed.

Cost effectiveness of correct dosing

Despite underdosing, in contrast to the other autoimmune liver diseases (primary sclerosing cholangitis and autoimmune hepatitis), liver transplant rates for primary biliary cholangitis in the UK have decreased by 50% over the last 20 years (*Figure 2*), emphasizing the effectiveness of ursodeoxycholic acid therapy (Webb et al, 2018). Optimizing the dose of ursodeoxycholic acid in partial responders would further decrease the increased morbidity associated with decompensated cirrhosis, reduce mortality and decrease the need for liver transplantation (*Figure 3*). Hence, optimizing the dose of ursodeoxycholic acid for individual patients would improve the cost effectiveness of ursodeoxycholic acid therapy by significantly reducing the high costs to the NHS of repeated hospital admissions and liver transplantation.

Conclusions

Studies show that the majority (50–60%) of patients with primary biliary cholangitis in the UK are underdosed with ursodeoxycholic acid, and unfortunately this trend has not changed over the past two decades. One third of partial responders when assessed at 1 year after starting treatment will respond if the correct dose is then prescribed, with a corresponding improvement in morbidity and mortality, and a major long-term cost saving to the NHS. Despite

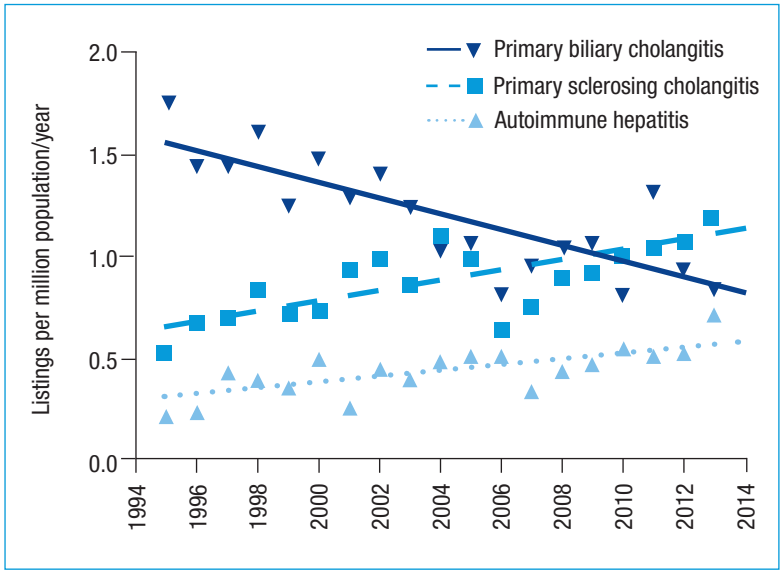

Figure 2. Adjusted listings for liver transplantation over a 20-year period from Webb et al (2018).

KEY POINTS

- Ursodeoxycholic acid is established as the first-line treatment of primary biliary cholangitis.
- The correct dosage of ursodeoxycholic acid is determined by body weight viz 13–15 mg/kg/day.
- Clinical response is based on specified improvements in serum liver tests including near normalization of the serum alkaline phosphatase level at 1 year. At least two thirds of patients with primary biliary cholangitis should respond to ursodeoxycholic acid after 1 year's treatment.
- Over a third of ursodeoxycholic acid partial responders became responders within 2 years after increasing the dose to recommended levels.
- A significant number of patients with primary biliary cholangitis in the UK are being underdosed, exposing them to increased morbidity, mortality and an increased chance of requiring liver transplantation.

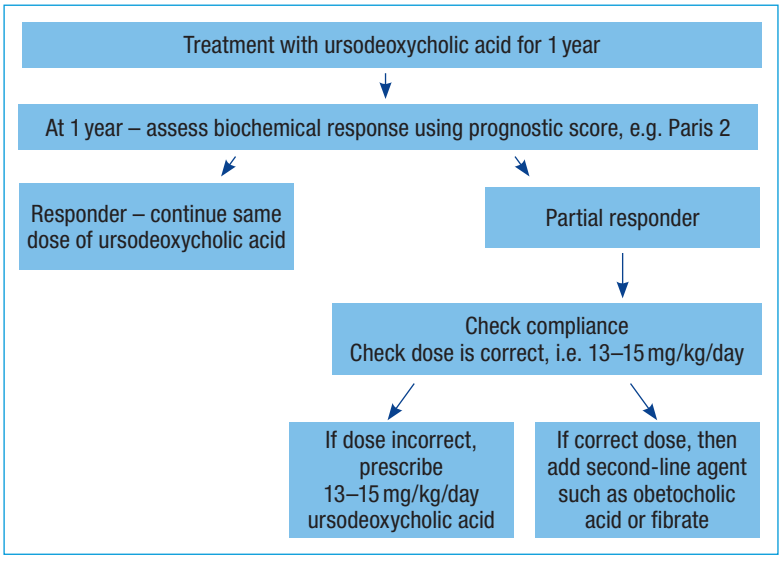

Figure 3. Management guideline for ursodeoxycholic acid dosage.

underdosing, orthotopic liver transplantation rates for primary biliary cholangitis in the UK are decreased by 50% over the last 20 years indicating the major long-term benefits of ursodeoxycholic acid therapy in reducing morbidity and mortality. There is a clear need to educate and inform doctors, nurses and, importantly, patients about the benefits of correct dosing in primary biliary cholangitis. **BJHM**

Conflict of interest: Dr RW Chapman has served on advisory boards and lectured on behalf of Dr Falk Pharmaceuticals and Intercept Pharmaceuticals.

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