**Supplementary Table 1 | Summary of previous therapeutic trials in PBC**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Details</th>
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<tr>
<td>Colchicine</td>
<td>A 2-year placebo-controlled trial (n = 90) to compare the efficacy of colchicine and UDCA in PBC. Clinical events, laboratory test results and liver histology were recorded at the beginning and end of the trial. Pruritus was reduced by both active drugs. Colchicine modestly improved liver function test results, whereas UDCA significantly decreased serum levels of aminotransferases, ALP and GGT compared with colchicine and placebo. Total serum bilirubin levels were decreased only by UDCA. Both colchicine and UDCA reduced serum cholesterol levels, and UDCA also reduced high-density lipoprotein cholesterol levels. UDCA significantly decreased ductular proliferation compared with colchicine or placebo. S1, S2, S5, S6, S7, S8, S9.</td>
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<td>D-Penicillamine</td>
<td>A prospective double-blind trial of 26 patients receiving D-penicillamine (250 mg four times a day), and 26 patients receiving placebo. There was no improvement in survival or symptoms after 28 months. Serum bilirubin and ALP levels increased equally in both groups. ALT and AST levels were lower in the D-penicillamine group, but serum albumin was also lower in this group. Liver histology worsened equally in both groups. Major adverse effects occurred in 31% of the patients receiving D-penicillamine and less serious adverse effects occurred in an additional 46% of these patients. S9.</td>
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<td>Prednisolone</td>
<td>A 3-year, placebo-controlled trial of prednisolone (n = 19) versus placebo (n = 17) in PBC. At 3 years, there was no significant difference in liver-related mortality between the groups. However, overall hepatic function was significantly worse in the placebo group (doubling in bilirubin, 6 g/L fall in albumin, de novo appearance of cirrhosis or symptoms of portal hypertension) (P &lt;0.01). No significant differences could be detected in bone mineral content. S4.</td>
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<td>Methotrexate</td>
<td>A placebo-controlled, randomized, multicentre trial to compare the effects of methotrexate 15 mg/m² body surface area (max dose 20 mg weekly) plus UDCA to UDCA alone in 256 AMA-positive patients without ascites, variceal bleeding, or encephalopathy; a serum bilirubin level &lt;3 mg/dL; serum albumin ≥3 g/dL, who had taken UDCA 15 mg/kg for at least 6 months. The median time from randomization to closure of the study was 7.6 years (range: 4.6–8.8 years). Treatment failure was defined as death without liver transplantation; transplantation; variceal bleeding; development of ascites, encephalopathy, or varices; a doubling of serum bilirubin to ≥2.5 mg/dL; a fall in serum albumin to &lt;2.5 g/dL; or histological progression by at least two stages or to cirrhosis. There were no significant differences between the groups in these parameters nor to the time of development of treatment failures. The trial was stopped early by the National Institutes of Health for reasons of futility. S6.</td>
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<td>Ciclosporin</td>
<td>A single-centre, double-blind, randomized controlled trial of methotrexate, 7.5 mg per week (n = 30), versus placebo (n = 30) for up to 6 years in PBC. Patients who received methotrexate had significantly lower on-treatment serum ALP, GGT, IgM and IgG, and lower AST and ALT levels after 24 months, a nonsignificant trend toward lower on-treatment pruritus scores, similar on-treatment Knodell inflammatory scores but nonsignificant trends toward lower Knodell fibrosis score and less ductopenia. A 2.9-fold (95% CI 0.85–10.25) increase in the rate of death or liver transplantation as a result of liver disease during or after the trial (P = 0.09) was observed in the methotrexate group. S7.</td>
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<td>Azathioprine</td>
<td>A prospective, randomized, double-blind, controlled trial of 25 patients assigned to receive either UDCA (500 mg daily) plus methotrexate (10 mg weekly) or UDCA plus placebo for a period of 48 weeks. Biochemical and histological changes were comparable in both groups at 48 weeks. The use of methotrexate in combination with UDCA was not followed by an additive benefit over UDCA alone. S5, S8.</td>
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A controlled prospective trial of 45 patients of whom 22 were given azathioprine 2 mg/kg and 23 received placebo. Throughout the trial, ALP, bilirubin, albumin and IgM values showed no significant change. Serial hepatic biopsy samples showed the development of cirrhosis equally in the two groups.

A multinational, double-blind, randomized clinical trial including 127 patients who received azathioprine and 121 who received placebo. The actual survival was slightly longer during azathioprine than during placebo treatment. Using Cox multiple regression analysis, the therapeutic effect of azathioprine was statistically significant \((P = 0.01)\), with azathioprine reducing the risk of dying to 59% of that observed during placebo treatment (95% CI 40–90%) or improving survival time by 20 months in the average patient. The analysis revealed that five variables independently implied poor prognosis: high serum bilirubin, old age, cirrhosis, low serum albumin, and central cholestasis.

**Budesonide**

A 2-year prospective, controlled double-blind trial of 20 patients (mainly with early-stage disease) treated with UDCA 10–15 mg/kg daily in addition to 3 mg budesonide three times daily (group A), and 19 patients (1 dropped out for personal reasons) treated with UDCA plus placebo (group B). The budesonide group had significantly larger decreases in liver enzymes, IgM and IgG levels, and a 30.3% improvement in the point score of liver histology (compared to a 3.5% deterioration in the placebo group).

A study of 22 patients with PBC who had been on UDCA (13–15 mg/kg daily) for a mean of 46 months and had shown a persistent elevation of ALP at least 2 times the upper limit of normal. Oral budesonide, 9 mg daily, was administered for 1 year and patients continued on the same dosage of UDCA. There was a significant, but transitory improvement in serum bilirubin levels \((P = 0.001)\) and a significant, but marginal improvement in serum ALP levels \((P = 0.001)\) with combination therapy. The Mayo risk score increased significantly \((P = 0.02)\) and there was a significant loss of bone mass \((P <0.001)\) of the lumbar spine. Budesonide appeared to add minimal, if any, additional benefit to UDCA, and was associated with a significant worsening of osteoporosis.

A 3-year prospective, randomized, open multicentre study of 77 patients with PBC (stages I to III) randomly allocated to budesonide 6 mg daily and UDCA 15 mg/kg daily or UDCA 15 mg/kg daily alone. Budesonide combined with UDCA improved liver histology, whereas the effect of UDCA alone was mainly on laboratory values.

**Abbreviations:** ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; AST, aspartate aminotransferase; UDCA, ursodeoxycholic acid

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