UDCA for NASH: End of the story?

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Non-alcoholic steatohepatitis (NASH) is estimated to affect about 1% of the European and North-American population. Longitudinal studies reported that the histological parameters worsen in one third of patients, which carries the risk of progression to cirrhosis [1]. The most physiological therapy of NASH is physical exercise and weight loss, and is especially indicated in overweight patients with insulin resistance [2]. However, treatments based on changes in lifestyle often fail, which provides the incentive for the continued exploration of drug therapies. Glitazones, which are PPAR-γ agonists and insulin-sensitizers, have proven promising in randomized clinical trials, but these drugs are associated with weight gain. Moreover, the cardiovascular safety of glitazones has been questioned [3].

In 1996, Laurin published a pilot study in which 24 NASH patients were treated with 13–15 mg/kg/day of ursodeoxycholic acid (UDCA) for 12 months [4]. The result was a significant decrease in mean serum concentrations of alkaline phosphatase (−8%), alanine transaminase (ALT) (−30%), and gamma-glutamyl transpeptidase (γGT) (−45%), as well as a decrease in the histological grade of hepatic steatosis.

Why should UDCA be beneficial in NASH? Three non-exclusive mechanisms can explain the benefits of UDCA. First, hepatocyte apoptosis is a pathogenic feature of NASH [5] and UDCA has well-known anti-apoptotic properties [6]. Second, TNF-α is increased in NASH patients [7] and aggravates the insulin resistance. UDCA has been reported to decrease serum TNF-α levels, at least in patients with primary biliary cirrhosis [8]. The third mechanism was deduced from experimental data, which showed that the taurine-conjugated UDCA (TUDCA) decreases endoplasmic reticulum stress [9] and that TUDCA improves muscle and hepatic insulin sensitivity in obese individuals [10].

When interpreted in light of this background, the results of a randomized controlled trial of UDCA in NASH reported by Lindor and colleagues were disappointing. Lindor enrolled 166 NASH patients, who received either UDCA 13–15 mg/kg/d or placebo for 2 years. Both groups achieved the same decrease in serum ALT concentrations at the end of the study. Similarly, both groups improved their degree of steatosis. Consequently, no measurable benefit could be attributable to UDCA. A smaller Swiss, randomized, controlled study reported no benefit of UDCA over placebo on histology in NASH patients [11]. There was a beneficial effect of UDCA on ALT in this trial, which was due to the absence of improvement of serum ALT levels in the placebo arm.

These mostly negative results raise the possibility that UDCA was not effective because its dosage was too low. Since the benefits of higher dosage of UDCA were reported for other diseases [12,13], two trials with higher dosage were launched. This issue of the Journal publishes the results of one study conducted by Ratziu et al. [14]. One hundred and twenty-six patients with biopsy-proven NASH at elevated ALT levels were randomized to receive either high-dose UDCA (28–35 mg/kg/d) or placebo for 1 year. The reduction of the mean ALT levels was significantly greater in the UDCA group than in the placebo group (see Table 1). High-dose UDCA was associated with a decrease in γGT and a reduction of FibroTest measures, which has γGT as one of its components and which was used as a surrogate marker for fibrosis instead of histological analysis. Serum glucose concentrations improved as did the insulin resistance (HOMA score) in the group treated with high doses of UDCA. (see Table 1) The adiponectin levels fell in both groups but the decrease was greater in the control (−22%) than in the high-dose UDCA group (−5%, not significant).

In the second trial, Leuschner et al. assigned 185 patients with biopsy-proven NASH to receive either high-dose UDCA (23–28 mg/kg/d) or placebo for 18 months [15]. High-dose UDCA failed to improve the histological parameters, the primary endpoint. The NASH activity score changed from 5.7 to 4.7 in the placebo group and from 5.6 to 4.3 in the high-dose UDCA group. Only γGT levels improved significantly after the high-dose UDCA for 18 months, whereas the ALT levels decreased in a comparable way in both groups (see Table 1).

How do these two trials compare? Apart from the ethnic differences in the sample populations, the dose of UDCA was higher in Ratziu’s trial than in Leuschner’s (28–35 vs. 23–28 mg, respectively) and the duration of treatment was longer in Leuschner’s study than in Ratziu’s (18 vs. 12 months, respectively). For the histological inclusion criteria, Riatzu used the score elaborated by Kleiner et al. [16], whereas Leuschner chose a modified Brunt score (17). The mean NASH activity score was higher in Leuschner’s trial.

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Table 1. Serum glucose concentrations and insulin resistance (HOMA score) improve in the group treated with high doses of UDCA.

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<tbody>
<tr>
<td>86</td>
<td>15</td>
<td>61</td>
<td>91</td>
</tr>
<tr>
<td>UDCA (N)</td>
<td></td>
<td>80</td>
<td>55</td>
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<tr>
<td>13-15 mg/kg/d</td>
<td>12-15 mg/kg/d</td>
<td>28-35 mg/kg/d</td>
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**UDCA DOSE**

<table>
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<tr>
<th>INCLUSION-CRITERIA</th>
<th>DURATION</th>
<th>ENDPOINT HISTOLOGY</th>
<th>ENDPOINT ALT</th>
<th>ENDPOINT METABOLISM</th>
<th>OTHER ENDPOINTS</th>
</tr>
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<tbody>
<tr>
<td>Elevated ALT 1.5 fold for at least 6 months</td>
<td>2 years</td>
<td>Single pathologist blinded to the sequence of the biopsy and to the assigned treatment. Severity of fatty infiltration, necroinflammation, and fibrosis were graded (0-3)</td>
<td>Steatosis UDCA vs placebo: Baseline mean 2.2 vs 2.1 change – 0.4 vs -0.3 in % - 18% vs -14%</td>
<td>BMI unchanged</td>
<td>γ-GT, UDCA vs placebo: Baseline mean 122 vs 126 change -62 vs +24 In % -51% vs. +19%</td>
</tr>
<tr>
<td>Biopsy-proven NASH: &gt;10% steatosis along with lobular necroinflammatory changes</td>
<td>2 years</td>
<td>Single pathologist blinded to the patient, sequence of the biopsies and assigned arm and scored the biopsies using the scoring system of Promrat et al. [22]</td>
<td>Activity index, UDCA vs placebo: Baseline mean 6.3 vs 5.8 change – 0.8 vs -0.02</td>
<td>BMI unchanged</td>
<td>γ-GT, UDCA vs placebo: Baseline mean 87 vs 91 change -52 vs -17 In % -60% vs. +19%</td>
</tr>
<tr>
<td>Biopsy-proven NASH: &gt;10% steatosis, hepatocellular injury (ballooning, dropout), lobular inflammation</td>
<td>1 year</td>
<td>Not assessed</td>
<td>Stage of fibrosis, UDCA vs placebo: Baseline mean 1.4 vs 1.0 change +0.3 vs +0.4</td>
<td>BMI unchanged</td>
<td>Glucose, UDCA vs placebo: Baseline mean 5.6 vs 5.6 Change -0.2 vs -0.1 In % -3.4% vs -1.4%</td>
</tr>
<tr>
<td>Elevated ALT &gt;50 IU/L on 3 occasions in 12 months</td>
<td>1.5 years</td>
<td>Single pathologist blinded to the treatment scored the biopsies using modified Brunt score [17] and NASH activity score [16]</td>
<td>Modified Brunt score, UDCA vs placebo: Baseline mean 7.0 vs 7.3 Change -1 vs -1 in % -14% vs. -14%</td>
<td>BMI unchanged</td>
<td>Glucose, UDCA vs placebo: Baseline mean 5.6 vs 5.6 Change -0.2 vs -0.1 In % -3.4% vs -1.4%</td>
</tr>
<tr>
<td>Biopsy-proven NASH according to a modified Brunt Score [17]</td>
<td></td>
<td></td>
<td>NASH activity score, UDCA vs placebo: Baseline mean 5.6 vs 5.7 Change -1.2 vs -1.0 in % -21% vs. -18%</td>
<td>BMI unchanged</td>
<td>BMI unchanged</td>
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In red, differences which were statistically significant ($p<0.05$).
than in Ratziu’s (5.6 vs. 5.15 in the high-dose UDCA arm and 5.7 vs. 4.88 in the placebo arm, respectively). The ALT improvement in the placebo group of Leuschner’s trial stands in contrast to that of Ratziu’s trial. Leuschner included patients with elevated ALT levels documented over a period of 3 months whereas Ratziu required documentation of elevated ALT on three occasions over a period of 12 months. This may have excluded patients with fluctuating ALT levels. The fact that more diabetic patients were enrolled in Ratziu’s trial than in Leuschner’s trial (39% in the UDCA arm and 25% in the placebo arm vs. 11% and 12%, respectively) may explain why Ratziu’s trial presented improved metabolic endpoints, albeit given in percentages. A comparison of the absolute numbers (serum glucose decreased from 5.6 to 5.47 with high-dose UDCA and increased from 5.5 to 5.7 with placebo) is less convincing. It is noteworthy that a trend towards lower serum glucose concentrations in the UDCA arm than the control arm was also noted in Leuschner’s trial (5.9–5.71 (−3%) vs. 5.6–5.52 (−1.4%), p = 0.193).

What message should be retained from these trials? The first message is that UDCA in monotherapy has no positive effect in NASH with the usual dose, and has only marginal and perhaps clinically irrelevant effects at a higher dose. But the story does not end there for bile acids. In a randomized controlled trial, we reported that vitamin E added to UDCA was better than UDCA monotherapy [11]. Since vitamin E has shown impressive effects in monotherapy in the treatment of NASH [18], a trial comparing vitamin E monotherapy with the vitamin E + UDCA combination is warranted. Bile acids – but not UDCA – regulate metabolism by binding to the nuclear hormone receptor farnesoid X and to a transmembrane bile acid receptor, TGR5. Activation of farnesoid X receptor improves insulin sensitivity and reduces circulating glucose and lipids levels [19]. TGR5 is an important regulator of glucose homeostasis and lipid metabolism and its activation stimulates energy expenditure and protects against obesity [20]. These actions of bile acids mimic those of lifestyle changes. The effects of non-UDCA bile acids in NASH should now receive some of the attention that we have, until now, reserved for UDCA.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References