SUBSTANTIATION OF USING THE URSODEOXYCHOLIC ACID IN THE TREATMENT OF NON-ALCOHOLIC STEATOHEPATITIS

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Key words: non-alcoholic steatohepatitis, treatment, ursodeoxycholic acid, physiological effects, evidence base

The actual prevalence of non-alcoholic fatty liver disease (NAFLD) is not exactly known due to the lack of highly reliable diagnostic blood tests and non-invasive imaging methods. NAFLD affects about one third of the adult population [10]. Thus, in studies using magnetic resonance tomography and spectroscopy, the incidence of NAFLD in the general population was 34%, although it was much higher when examining patients with obesity [17]. Even with normal values of hepatic transaminases, the presence of type 2 diabetes mellitus (DM) additionally increases the risk of non-alcoholic steatohepatitis (NASH) in patients with obesity, although there is no reliable data on its true prevalence. In a relatively small study of 103 patients with type 2 diabetes and normal transaminases, the frequency of NAFLD was 50%, and more than half of them had NASH [13, 14]. In a large population-based study involving more than three thousand middle-aged people from Rotterdam who underwent ultrasound screening and transient elastography, it was shown that 17.2% of patients with type 2 diabetes had marked liver fibrosis [12]. This is a very alarming fact, since increased morbidity and mortality in NASH from cirrhosis, hepatocellular carcinoma, and cardiovascular diseases are closely related to the severity of liver fibrosis [6].

The basis and mandatory first stage of prevention and treatment of NASH is the modification of lifestyle and nutrition.

Many patients have difficulty losing weight, so there is often a need to use targeted pharmacotherapy. Currently, there is not a single drug for the treatment of NASH, approved and recommended by the US Food and Drug Administration

(FDA). Nevertheless, a large number of pharmacological agents are now in the stage of in-depth clinical studies [6].

In a number of randomized clinical studies using ursodeoxycholic acid (UDCA), a decrease in liver steatosis was obtained, as well as a positive biochemical dynamics in NASH.

The effectiveness of UDCA in NASH is based on its properties (Fig. 1).

The rationale for the use of UDCA for the treatment of NASH are also those physiological functions that it performs in the human body: providing bile flow; improving the absorption, transport and elimination of fat-soluble vitamins, steroids, toxic metabolites and xenobiotics; activation of nuclear receptors, that is, the function of signaling molecules; regulation of glucose and lipid metabolism; induction of drug metabolism in the liver; activation of the TGR5 G-protein coupled receptor and stimulation of the energy metabolism of brown adipocytes. Recently, a TGR5 bile acid membrane receptor has been discovered that stimulates the production of incretins (peptide hormones that are secreted by intestinal L-cells in response to food intake and stimulate insulin production by pancreatic β cells before the blood glucose level rises). Bile acids, as was recently shown, act as signaling molecules with systemic endocrine functions. They activate protein kinase pathways, are ligands for TGR5 and thus regulate their own enterohepatic circulation, as well as homeostasis of glucose, triglycerides and energy. This function can serve as a promising model for the development of directional drugs for the treatment of metabolic diseases such as obesity, type 2 diabetes, hyperlipidemia, and atherosclerosis [2].

When comparing the effectiveness of UDCA and Clofibrate in the treatment of NASH, it is proved that only UDCA at a dose of 13–15 mg/kg/day during the year leads to a decrease in the indicators of cytolysis and cholestasis enzymes, to a decrease in the severity of liver steatosis according to the results of histological examination [3, 5]. The results of some of the recent studies on the effectiveness of UDCA in NASH are presented in Fig. 2.

The administration of UDCA in a dose of 13–15 mg/kg, according to another study, also had a positive effect on the biochemical indices of cytolysis and

cholestasis. UDCA also reduces the severity of steatosis. Data were obtained indicating a positive effect of UDCA on the ratio of serum markers of fibrogenesis and fibrolysis [1].

When NASH, it is advisable to use UDCA in combination with tocopherol (400 IU 2 times a day), which has an antioxidant effect. Such a combination therapy significantly reduces the severity of steatosis, the activity of inflammation and fibrosis, according to histological studies (Fig. 2, 3, 4) [8, 9]. After 12 months of treatment, patients had a significant decrease in transaminase and-glutamyl transpeptidase levels, whereas in the placebo group, these values even increased. In addition, during therapy with high doses of UDCA, reliable normalization of carbohydrate metabolism parameters was recorded: HOMA index, glucose level, glycosylated hemoglobin, and insulin in the blood. Also, when using high doses of UDCA, there was a decrease in the progression of liver fibrosis, according to Fibrotest, compared with the placebo group.

Recently, data have been obtained on the need to increase the dose of UDCA with NASH to 25–30 mg/kg. High doses of UDCA provide a significant decrease in markers of cytolysis and cholestasis without increasing the risk of side effects [16].

In case of dyslipidemia, UDCA can be combined with statins. This combination has been shown to be well tolerated and allows for a more pronounced reduction in the cholesterol level of low-density lipoproteins with a lower dose of simvastatin or atorvastatin. With an initially elevated serum transaminase level, adherence to statin therapy with UDCA at a dose of 15 mg/kg/day. It often allows to achieve normalization of ALT and AST. Published data indicate that with the joint prescription of statins and UDCA, a reduction in the statin dose is possible, while maintaining a pronounced hypolipidemic effect in patients with dyslipidemia with NASH. The combination of UDCA with statins also has a beneficial effect on the course of gallstone disease in NAFLD [2, 11].

Thus, UDCA is one of the pathogenetically substantiated and effective means of treating NASH.

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The article provides brief epidemiological data on non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, emphasizing the danger of steatohepatitis, progression of which may cause the development of hepatocellular carcinoma. The properties of ursodeoxycholic acid, which are the basis for its use in a treatment of non-alcoholic steatohepatitis, are analyzed in detail, such as cytoprotective, antioxidant, antifibrotic ones, effects on apoptosis, etc. The authors presented the results of the main evidence-based studies demonstrating the effectiveness of ursodeoxycholic acid and its combinations with other drugs in the treatment of non-alcoholic steatohepatitis.

Fig. 1. Short-term and long-term clinical effects of UDCA (by S. V. Morozov et al., 2011 [4]).

Fig. 2. Clinical effects of UDCA at a dose of 25–30 mg/kg/day upon NASH. 1 [15]; 2 [7]; 3 [15]; 4 [15]. HD-UDCA — high doses of UDCA.

Fig. 3. Dynamics of the index of histological activity in the treatment of NASH (by J. F. Dufour et al., 2006 [9]).

Fig. 4. The dynamics of the severity of liver fibrosis in patients with NASH during therapy with high doses of UDCA compared with placebo (by V. Ratziu et al., 2011 [15]):

А — absolute mean change;

Б — relative mean change;

В — absolute mean change in patients with fibrosis at the stage of selection;

Г — absolute mean change in patients without fibrosis at the selection stage.

HD-UDCA — high doses of UDCA.