Search of New Opportunities of Pharmacological Protection at the Early Stages of a Non-Alcoholic Fatty Liver Disease Associated With Obesity and Metabolic Syndrome

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***Abstract*—This article provides the rationale for the pharmacological correction of non-alcoholic fatty liver disease. This is due to the fact that non-alcoholic steatohepatosis of the liver is a slowly progressing disease. Most often, non-alcoholic steatohepatosis progresses to non-alcoholic steatohepatitis, less commonly fibrosis. It should also be noted that if you do not intervene during the disease, steatohepatitis can transform into cirrhosis, bypassing the stage of liver fibrosis. At the same time, the prevalence of non-alcoholic fatty liver dis-ease progressively increases with the age of patients. Thus, the maximum prevalence of non-alcoholic steatosis was noted in the age group of 70–80 years, non-alcoholic steatohepatitis in patients 50–59 years old. Thus, pharmacotherapy of non-alcoholic fatty liver disease should be based on the basic principle of geriatric pharmacotherapy: safety if long-term use of drugs is necessary. In this regard, it substantiates the possibility of using the essential amino acid methionine and flavolignan complex of the fruits of milk thistle for the correction of metabolic conditions associated with non-alcohol steatohepatitis.**

Keywords—non-alcoholic fatty liver disease, non-alcohol steatohepatitis, geriatric pharmacotherapy, methionine, flavolignan complex

I. INTRODUCTION

Non-alcoholic fatty liver disease (NFLD) is currently one of the most common chronic diseases in hepatology, leading to a deterioration in the quality of life and disability. First of all, this is due to the high risk of progression of NFLD with the development of non-alcoholic steatohepatitis (NASH) [1].

NFLD is also one of the key risk factors for cardiovascular disease and its complications [2, 3].

II. RESULTS AND DISCUSSION

According to established criteria, NFLD combines a range of clinical and morphological changes in the liver represented by steatosis, non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis, developing in patients who do not drink alcohol in hepatotoxic doses (no more than 40 g of ethanol per day for men and not more than 20 g for women) [4].

According to the researchers, if you do not interfere with the natural course of the disease, then in 12-14% of NFLD transforms, in 5-10% of cases, into fibrosis, up to 5% of cases, fibrosis passes into cirrhosis of the liver, and in 13% of cases NASH immediately transforms into cirrhosis [5].

According to published data, up to 80% of cases of cryptogenic cirrhosis are the outcome of NFLD [6].

According to the data of foreign literature, there have been 1.6 billion patients with NFLD in the world recently. In various populations, from 6.3 to 33% of the population have NFLD [7].

The results of epidemiological studies carried out in the current decade indicate that the prevalence of NFLD over the past 20 years has increased by almost 2 times. Young people are especially at risk; thus, among adolescents, the prevalence of NFLD increased by 17.4% [8].

According to forecasts of the World Health Organization, NFLD will occupy the 1st place in the structure of liver diseases by 2020 [9].

For a long time there was no data on the prevalence of NFLD in Russia. A population study DIREG_L 01903, conducted in the Russian Federation in 2007 with the participation of 30 754 people, showed that 27% of all

patients who turned to general practitioners had NFLD: steatosis was observed in 77%, NASH - in 20%, cirrhosis liver - in 3% of patients [10].

Moreover, the prevalence of NAFLD progressively increased as the age of patients increased from 2.90% (12-17 years) to 42.96% (60-69 years). The maximum prevalence of non-alcoholic steatosis was noted in the age group of 70–80 years (34.26%), non-alcoholic steatohepatitis in patients 50–59 years old (10.95%) [10].

In the course of the conducted epidemiological studies, a direct relation-ship between NFLD and obesity and components of the metabolic syndrome (MS) was confirmed, which does not contradict the world data, according to which the frequency of NFLD in patients with type 2 diabetes (T2D) and obesity varies from 70 to 100%. Moreover, T2D or impaired glucose tolerance (IGT) are noted in 10–75%, obesity in 30–100%. hypertriglyceridemia in 20–92% of patients with NFLD [4, 9].

A number of researchers are currently proposing to classify NFLD as another component of MS [11, 12].

NFLD does not have a specific clinic, it is asymptomatic and often diagnosed already at the stage of NASH. However, standardized therapeutic approaches to the management of NFLD patients have not been developed, and currently there are no strictly regulated treatment regimens for NFLD.

All existing recommendations emphasize that only lifestyle changes are the most evidence-based way of influencing liver steatosis. However, no drug was approved by the FDA as a treatment for NFLD with evidence-based assessment of its effect on the histological picture.

Therefore, in clinical practice, it is advisable to focus on early prevention of the metabolic syndrome and, accordingly, NFLD, as one of its components.

According to the recommendations of the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO) pharmacotherapy can be prescribed to patients not only with NASH, but also to patients with a less severe form of NFLD, especially with the presence of markers that contribute to the progression of the disease (diabetes, metabolic syndrome, a steady increase in ALT) and mandatory weight correction.

The rationale for prescribing a particular drug (or combination) is its ability to affect one or more pathogenetic mechanisms of NFLD. In this correspondence, groups of preparations containing a flavolignan complex and amino acid derivatives can be considered.

Methionine stimulates the formation of biologically active substances, activates the action of hormones, vitamins, enzymes, promotes the synthesis of proteins, prevents fatty liver, lowers blood cholesterol, has an antitoxic effect, strengthens cell membranes, reduces the effects of poisons on the liver and other fabrics. Recently, it has been widely used as a drug that improves liver function in NFLD [13, 14].

Methionine metabolism is shown as a scheme in Fig.1.

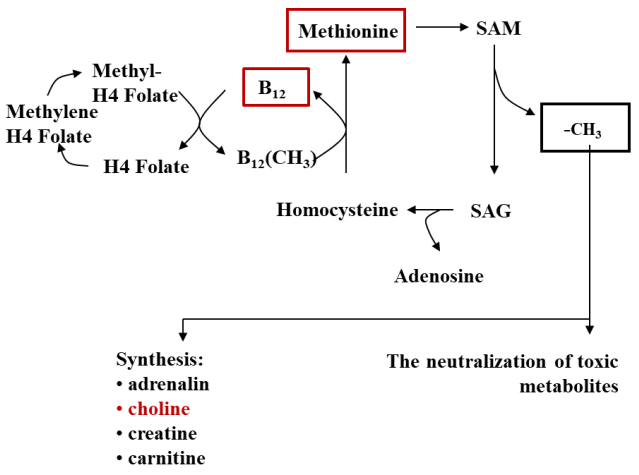

Fig. 1. Methionine Metabolism Scheme.

As can be seen from the scheme of Figure 1, when ingested, methionine is metabolized and converted to S-adenosylmethionine (SAM), which is a source of labile methyl groups. SAM transmethylation reactions are used to synthesize choline, an increase in the content of which promotes an increase in the synthesis of endogenous phospholipids and a decrease in the deposition of neutral fat in the liver, as well as normalization of lipid metabolism, which is the basis of the pharmacotherapy of non-alcoholic steatohepatosis and pre-vents its progression [15-17].

In addition, with atherosclerosis, methionine reduces the concentration of cholesterol and increases the content of phospholipids in the blood, which has a beneficial effect in the correction of MS [13].

Thus, the use of methionine for the complex treatment of diseases such as non-alcoholic steatohepatosis and atherosclerosis is promising in modern geriatrics, solving the problem of polypharmacy.

Medicines that are containing flavolignans of the milk thistle fruit are the most widely used herbal remedies for liver diseases. Only in Europe, the cost of these drugs is about $ 180 million annually [18, 19].

Milk thistle (S. marianum) fruit contain a complex of flavolignans, including silybin, silichristin, silidianin and their stereoisomers, and providing their hepatoprotective effect. The main component of the silymarin complex is silybin [20].

The mechanism of the hepatoprotective action of flavolignans of the fruits of thistle spotted is presented in Figure 2.

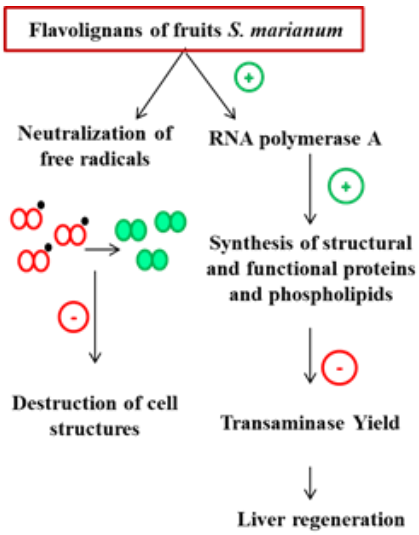

Fig. 2. The mechanism of hepatoprotective action of flavolignans of S. marianum fruits.

Figure 2 shows that the mechanism of hepatoprotective action is that silybin neutralizes free radicals, preventing the destruction of cellular structures, specifically stimulates RNA polymerase A and activates the synthesis of structural and functional proteins and phospholipids in damaged hepatocytes. Stabilization of the hepatocyte membrane prevents the release of transaminases, which accelerates the regeneration of the liver [21].

III. Conclusion

Taking into account the low toxicity of drugs with plant materials and, as a consequence, the possibility of their long-term use without significant side effects, for preventive purposes, as well as for the treatment of chronic diseases, the use of extract from S. marianum fruits as an API of a geriatric drug aimed at pharmacotherapy of steatohepatosis is advisable.

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