



Liver Fibrosis - Modern Methods of Diagnostics and Drug Correction

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ABSTRACT: Liver fibrosis is a local or diffuse increase in the amount of connective tissue, extracellular matrix (collagen fibrous tissue in the perisinusoidal space) and the main pathway for the progression of chronic diffuse liver diseases. In the early stages of fibrosis, clinical manifestations are absent, and only a histological examination of a biopsy specimen reveals an excessive accumulation of connective tissue. In the future, fibrosis leads to the formation of nodes of regenerates, vascular anastomoses - to the formation of cirrhosis of the liver.

KEYWORDS: Liver fibrosis, portal hypertension, liver cirrhosis, hepatocellular carcinoma.

Relevance of the problem:

Over the past decades, a lot of both clinical and experimental studies have been devoted to the assessment of liver fibrosis (LF). Attempts have been made to standardize the rules for managing patients with advanced fibrosis and cirrhosis of the liver (LC), and the tactics of using a number of pathogenetic drugs have been determined. However, the issues of fibrosis progression as a prognostic marker of fatal complications and methods of correcting such disorders remain unresolved. In many respects, the results of the studies carried out remain rather contradictory, which significantly complicates the work of the clinician. Mortality from end-stage LF - cirrhosis - ranks 9th in the world among all causes of death and 6th among people of the most working age, ranging from 14 to 30 cases per 100 thousand population.

Mechanisms of LF formation: The mechanism of LF development follows from the versatility of the morphological reaction of the liver to damage, namely: steatosis, pigment deposits, thrombosis, apoptosis, necrosis, adaptation, proliferation of hepatocytes and fibrotic changes proper. Moreover, regardless of the etiological factor, only the severity of fibrogenesis determines at what stage the disease is, i.e. fibrosis is precisely the indicator that reflects the rate of progression of chronic diffuse liver damage.

New views on the formation of LF and LC processes consider the fact that fibrosis is currently not a one-way ticket to cirrhosis: regression, reverse development is possible [2,4]. The evolution of fibrosis in the LC is not just a process of scarring and replacement by connective tissue, but part of chronic liver disease, including inflammation, angiogenesis, remodeling and collagen formation. That is, the leading factor in the formation of LC is not the growth of connective tissue, but

angiogenesis. Thus, in the experiment, the prevalence of fibrosis correlated with the vascular indicator of portal hypertension HVPG (hepatic venous pressure gradient). In fact, the severity of fibrosis and the size of the nodes are predictors of significant portal hypertension (PH) (more than 10 mm Hg), which is associated with further prognosis of the disease. Based on the known data on the structural features of the portal bed, its connections with other vascular systems of the body, as well as information on the factors affecting the state of the vascular wall, it is possible to formulate the main physiological mechanisms that determine the level of pressure in the portal vein [5, 6]. These include: 1. Intrahepatic and portal vascular resistance. 2. The volume of blood in the portal vascular bed of the liver. 3. The state of the cardiovascular system.

Intrahepatic and portal vascular resistance This most important mechanism for maintaining portal pressure is influenced by:

1. The relationship of the cells of the sinusoidal compartment (Ito cells, Kupffer macrophages, endotheliocytes). Ito cells, being subjected to the regulatory influences of the autonomic nervous system (ANS), vasoactive substances, cytokines, chemokines, integrins, are able to contract, changing the lumen of the sinusoids. In this case, endothelial cells play the role of sphincters. Macrophages, in turn, secrete vasoactive substances that affect the functional activity of Ito cells and endothelial cells [7, 8].

2. The state of the ANS. VNS mediators have a direct effect on the receptors of sinusoidal cells, as well as vessels of the intrahepatic and general vascular bed.

3. The ratio of humoral-metabolic factors (vasoactive substances). Vasodilators (nitric oxide, carbon monoxide, prostacyclin, glucagon, prostaglandin E₂, atrial natriuretic hormone) and vasoconstrictors (endothelin ET₁, ET₂, adrenaline, angiotensin II, vasopressin, cytokines - interleukin IL-1, serotonin, mast cells) vascular wall.

4. Rheological properties of blood in sinusoids and intrahepatic vessels. The degree of fibrotic disorders correlates with the severity of microcirculatory disorders both at the level of large vessels of the liver and at the sinusoidal stage, exacerbating the state of hypoxia, radical oxidation, endothelial dysfunction and stimulation of fibrogenesis under these conditions.

The volume of blood in the portal vascular bed of the liver. It is known that the amount of portal blood flow depends on two main factors:

1. Pressure gradient between the capillary system of the abdominal cavity and the sinusoidal bed of the liver. It is important to emphasize that the pressure level in the first capillary network is 110 mm Hg. Art., in the second - only 10. Therefore, the main role in changing the portal blood flow is played by the capillary system of the abdominal organs, which, in fact, is a powerful "physiological valve" that regulates the difference in systemic and intrahepatic pressure [9].

2. Hydromechanical resistance of the vessels of the portal system, the value of which is determined by the total resistance of the first and second capillary systems. A change in resistance at the level of at least one capillary system leads to a change in the total resistance and an increase or decrease in portal blood flow. Significant fluctuations in hydromechanical resistance occur as a result of changes in the lumen of blood vessels under the influence of nervous and humoral regulation.

The state of the cardiovascular system. Most essential in maintaining portal pressure are:

1. Type of central hemodynamics. About 30% of the minute volume of blood flow normally flows through the portal bed. An increase in the latter in hyperkinetic type of central hemodynamics can lead to an increase in pressure in the portal vein due to an increase in portal blood flow [29,30].

2. Cardiac output and blood pressure level. The blood flow in the portal vein system depends on the pressure gradient between the celiac artery, the sinusoidal system and the hepatic veins. The level

of blood pressure in the mesenteric arteries, in turn, is related to the value of cardiac output, i.e. with systolic pressure. An increase in the latter can probably lead to an increase in pressure in the portal system due to an increase in portal blood flow, which leads to compensatory stimulation of the renin-angiotensin-aldosterone system (RAAS). The imbalance between the subtle physiological mechanisms that affect fibrogenesis and the associated state of blood flow in the portal vein lead to the occurrence of PH and LC.

According to modern genetic studies, the significance of gene polymorphism in the progression of fibrosis in chronic liver diseases has been established. The formation of fibrotic changes in the organ is based on a quantitative and qualitative imbalance of the components of the extracellular collagen matrix (ECM). Already at a moderate 2nd stage of fibrosis, ECM of the liver (collagens [1st, 3rd and 4th types], fibronectin, undulin, elastin, laminin, hyaluronan and proteoglycans) exceeds normal values by 3-4 times, which is due to both by its intensive synthesis and by a decrease in the degradation of its elements [10]. The main source of ECM in damaged liver tissue is hepatic stellate cells (HSC), which are normally located in the Disse space. As a result of long-term chronic damage of any nature, the activation of HSC develops, their differentiation into myofibroblast-like structures with contractile, pro-inflammatory and fibrogenetic characteristics. Activated HSCs migrate and localize in the lesion focus, while secreting a mass of ECM. An important fact is that a number of other liver cells, such as myofibroblasts from small portal vessels, may also have a fibro-producing ability, which is activated around the biliary tract of the liver during cholestasis, which leads to additional accumulation of collagen. In general, cholestasis fundamentally changes the prognosis of liver disease, being an independent factor in fibrosis. In addition, HSC and portal myofibroblasts differentiate into specific cells that respond to the stimulation of apoptosis. The scientific and possibly practical importance of each cell type in LF may depend on the etiology of the hepatocellular injury. Thus, HSC is the main unit involved in fibrogenesis of the pericentral region, and portal-located myofibroblasts prevail in liver damage around the portal tracts. It should be noted that in the process of fibrogenesis there is a complex interaction between different types of liver cells [11,30].

The immediate factors controlling fibrogenesis are universal and, in some cases, specific cytokines produced by the cells of the sinusoidal compartment and regulating the inflammatory response to damage to hepatocytes. Known stimulators of fibrogenesis include monocytic chemotactic protein type 1, growth factor TGF- β 1, which promotes the transformation of HSC into myofibroblast-like cells, stimulating ECM synthesis and inhibiting its degradation. That is why the search for drugs that affect TGF β 1 continues, which could significantly reduce the rate of fibrosis [12]. Fibrogenic substances also include a powerful mitogen of HSC - PDGF, which leads to a violation of their regulation in the liver with the subsequent progression of fibrotic changes. At the same time, pro-inflammatory IL-10 and interferon- γ have a powerful antifibrotic effect [13, 30]. Cytokines with vasoactive properties also play an important role in the formation and progression of LF. So, vasodilating substances, such as nitrogen oxide and nitrite, relaxin, have antifibrotic properties, while vasoconstrictors norepinephrine and angiotensin II, which, according to a number of authors, play a dominant role in liver fibrogenesis, contribute to the acceleration of the pathological process of connective tissue synthesis in liver. The powerful vasoconstrictor endothelin-1 also stimulates the rate of progression of fibrotic changes in the liver tissue by acting on type A receptors. Thus, the pathogenesis of LF is currently regarded as an evolutionary process that includes intimate interactions of cells of the portal continuum and is a sequential chain of events: damage, activation of fibrosis-producing cells, endothelial dysfunction, development of intrahepatic (sinusoidal) PG, stimulation of angiogenesis, and subsequent accumulation of connective tissue. tissue in the organ. Accordingly, the predictors of active fibrogenesis will be not only factors that stimulate the growth of connective tissue, but also the reasons that aggravate the above factors of this multilevel process [14].

LF predictors:

1. Cholestasis in all forms.
2. Age over 45, because by this time, a lot of connective tissue accumulates on its own and the processes of replacement fibrogenesis proceed faster.
3. Male gender as a risk factor for PH
4. Viral load during HBV infection.
5. Iron overload syndrome.
6. Alcohol abuse.
7. Insulin resistance.
8. Uncorrectable portal hypertension.
9. Concomitant heart failure.

LF assessment methods. Currently, there are many methods for assessing fibrosis, which can be divided into several groups:

I. Laboratory methods

1) Direct markers of fibrosis - characterize the metabolism of the extracellular matrix (fibrogenesis and fibrinolysis) and / or changes in the HSC: hyaluronic acid is a polysaccharide present in ECM and increasing in the serum of patients with liver fibrosis; procollagen peptides, N-terminal peptide of procollagen III - collagen degradation product; collagens IV and VI, matrix metalloproteinases - a family of enzymes that break down proteins of the cellular matrix, when such proteins are in excess (fibrinolysis); TIMP-I - tissue inhibitor of metalloproteinase-1, indirectly promoting the synthesis of matrix proteins; YKL-40 - glycoprotein involved in the cleavage of ECM; laminin and pepsin-resistant fragment of laminin are the main non-collagen glycoproteins, the serum level of which increases in chronic liver diseases regardless of etiology and reflects the presence of perisinusoidal fibrosis.

2) Indirect markers of fibrosis. These are traditional serum markers, i.e. molecules released into the bloodstream due to the inflammatory process in the liver: aminotransferase: ALT (the most sensitive and specific indicator of hepatocellular damage [inflammation and necrosis of hepatocytes] and AST; ratio of AST / ALT levels (De Ritis coefficient); molecules synthesized, regulated or secreted by the liver, for example:

a) apolipoprotein A1. It was found that with an increase in the stage of fibrosis, the serum level of apolipoprotein A1 decreases;

b) alpha-2-macroglobulin (A2M). Increased A2M is a marker of the severity of the inflammatory process in the liver;

c) the number of platelets. It is used as an indicator of the severity of fibrosis, although it also reflects the severity of hypersplenism;

d) haptoglobin. Binds free hemoglobin (released from erythrocytes), is an important acute phase reactant. Has a negative relationship with LF. Decreased haptoglobin is a marker of the severity of the inflammatory process in the liver;

e) gamma-glutamyltranspeptidase (GGTP). There are 5 known pathological processes that increase the activity of GGTP: cytolysis, cholestasis, alcohol intoxication, tumor growth in the liver, exposure to hepatotoxic drugs (drug hepatitis, etc. fibromax test, steatoscrin, etc.) [15].

II. Instrumental methods for assessing LF

1) Imaging methods of examination. The widespread and available methods of visual non-invasive examination (ultrasound diagnostics and computed tomography) can be used to establish the diagnosis of LF, signs of PH, a number of vascular disorders (Doppler ultrasonography of the vessels of the portal system), but their diagnostic information is low.

2) Liver elastography. Elastography is a non-invasive technology to improve the visualization of soft tissue inhomogeneities by their shear characteristics. Additional pressure is applied to the tissue under study, due to unequal elasticity, heterogeneous tissue elements are reduced to varying degrees. The speed of propagation of elastic waves is determined by the elasticity of the liver tissue, which makes it possible to identify pathological areas in the organ. Indirect instrumental assessment of the severity of fibrosis by measuring the elasticity of the liver using the "FibroScan" apparatus is based on the generation of low-frequency oscillations transmitted to the liver tissue. The principle of the technique is the use of low-frequency oscillations to quantify elasticity as an indicator of the state of the liver and the percentage of connective tissue in it. A positive correlation has been proven between the results obtained with elastography and such a leading diagnostic procedure as liver biopsy [16,17]. Magnetic resonance elastography can be considered promising - a direct method for determining liver density, which makes it possible to determine F0, which proves the high accuracy of assessing fibrosis.

3) Liver biopsy. Based on the results of this procedure, it is possible to diagnose LF with a fairly high degree of specificity. Such an important invasive study is carried out only in specialized medical institutions, and requires high professionalism of the hepatologist-clinician and pathomorphologist. We must not forget that complications may develop during hepatobiopsy (up to 3% of cases).

There are also certain difficulties, since in 15–35% of cases, when performing a puncture biopsy of the liver, unchanged liver tissue is obtained, in 1.5% - uninformative material [18–20].

LF classification. The LF classification, which is used by most authors to date, was proposed at the 1994 hepatology congress in Los Angeles. She considers the presence of fibrosis, the stage of the disease: • 0 - no fibrosis; • 1 - mild periportal fibrosis; • 2 - moderate fibrosis with portoportal septa; • 3 - severe fibrosis with portocentral septa; • 4 - LC. All subsequent classifications include the above as an integral part, having features for certain nosological forms [21, 22].

LF therapy principles. Back in 2003 R. Safadi and S.L. Friedman developed the principles of ideal antifibrotic therapy, which should include the impact on all pathogenetic links of fibrogenesis. The main directions of antifibrotic therapy were the following:

I. Elimination of the etiological factor (see table), which includes:

- Treatment of chronic viral infection;
- Cancellation of drugs of hepatotoxic action;
- elimination of alcohol intake;
- normalization of metabolic and metabolic disorders;
- eradication of parasitic invasion;
- elimination of biliary obstruction.

II. Elimination of inflammatory changes in the liver, including:

- preparations of ursodeoxycholic acid (UDCA);
- glucocorticosteroids and immunosuppressants;
- antagonists of cytokine receptors;

- angiotensin-converting enzyme inhibitors;
- inhibitors of cytochrome P450 (metyroline);
- selective inhibitors of COX-2;
- blockers of Kupffer's cells.

III. Inhibition of HSC activation:

- antioxidants (vitamin E, phosphatidylcholine);
- cytokines;
- antagonists of endothelin receptors;
- silymarin;
- herbal preparations (silymarin);
- antagonists of cellular "fibronectin".

IV. Suppressing the effects of activated HSCs:

1. Suppression of antiproliferative activity: antagonists of cytokine receptors; inhibitors of lipogenase, tyrosine kinase; simvastatin; pentoxifylline; paramycin.

2. Antifibrotic action: propyl hydroxylase inhibitors; growth factor of hepatocytes; IL-10; transforming growth factor- β 1 antagonists; tissue protease inhibitors; angiotensin converting enzyme inhibitors; relaxin; halofuginone.

3. Anti-contraction action: antagonists of endothelin receptors; donors NO.

V. Increase in tissue repair: antagonists of transforming growth factor- β 1; relaxin; metalloproteinases;

VI. Stimulation of cellular apoptosis: gliotoxin; "Integrated" antagonists. At the same time, the list of directions for the treatment of LF is mostly more promising and cannot be adequately applied in clinical practice. Therefore, the search for new approaches to the correction of this condition remains extremely urgent.

To date, no standards for the treatment of LF have been developed, although there are a number of experimental research models.

The main approaches to the treatment of fibrosis:

- treatment of the underlying disease or interruption of the pathogenetic chain in cases of unknown etiology of chronic liver diseases (autoimmune diseases, for example) in order to eliminate the etiological factor of fibrosis [23–26];
- decrease in the activity of the inflammatory process in the liver;
- "inhibition of activation", stimulated apoptosis of HSC;
- activation of fibrolysis mechanisms for the destruction of excess ECM proteins;
- impact on GHG. drugs used for LF therapy.

All drugs for the treatment of liver fibrosis can theoretically be divided into two large groups - drugs acting on specific mechanisms of fibrogenesis, and drugs of nonspecific action [27,30].

Drugs acting on specific mechanisms of fibrogenesis include:

- interferons;
- synthetic analogs of nucleosides;

- UDCA;
- drugs that reduce the concentration of TNF- α (pentoxifylline, glycyrrhizic acid, biguanides);
- drugs that suppress excessive activation of macrophages and lower the level of TGF- β (angiotensin receptor inhibitors);
- endothelin antagonists (ambrisentan, bosentan, sitaxentan, tesosentan);
- inhibitors: caspase (GS9450); apoptosis (TRO19622); phosphodiesterase (ASP9831).

Nonspecific drugs include:

- membrane stabilizers and antioxidants (succinic acid preparations);
- flavonoids;
- phosphatidylcholine.

To effectively influence the multicomponent mechanism of development of fibrotic changes in the liver, it is advisable to use drugs that affect most of the significant stages of fibrogenesis. That is why one of the points in the basic requirements for an ideal hepatoprotector (according to R. Preisig) is adequate suppression of fibrogenesis. Thus, drugs such as UDCA, essential phospholipids and glycyrrhizic acid, vitamin E, silymarin, and S-adenosyl-L-methionine, inhibit the activation of HSC, protect hepatocytes from apoptosis, block the synthesis of TGF- β and thus contribute to a decrease in experimental hepatic fibrosis.

UDCA—hydrophilic non-toxic tertiary bile acid, formed under the action of bacterial enzymes from 7-keto-lithocholic acid coming from the small intestine. Ursodeoxycholic acid is currently the only biliary rheocorrector. Moreover, bile acid preparations are assessed by the US Food and Drug Administration (FDA) (FDA)—the only ones registered as a medicinal product. The antifibrotic effect of UDCA has been proven in cholestasis, when it reduces the release of cytochrome C, alkaline phosphatase and lactate dehydrogenase, inhibits the activity of HSP and perisinusoidal collagen formation, eventually preventing the development of LF. There are also a number of additional effects of UDCA, indirectly associated with antifibrotic action: *cytoprotective* - due to the presence of hydrophilicity, it improves the fluidity of the phospholipid bilayer of the hepatocyte membrane, restores the structure of cells and protects them from damage; *antioxidant* - UDCA prevents oxidative damage to liver cells and biliary tract due to blocking the release of free OH radicals, inhibits lipid peroxidation; *hepatoprotective* - UDCA forms double molecules that are incorporated into the phospholipid bilayer of the hepatocyte membrane, as a result, its structure is stabilized; *immunomodulatory* - the synthesis of immunocompetent IgM decreases, to a lesser extent - IgG, the expression of histocompatibility antigens on hepatocytes and cholangiocytes decreases, which in turn prevents the activation of cytotoxic T-lymphocytes, and also reduces the production of autoantibodies and helps to reduce immunopathological reactions; *antiapoptotic*—regulation of apoptosis, due to a decrease in the concentration of ionized Ca + 2 in cells, the release of cytochrome C from mitochondria is blocked, which in turn prevents the activation of caspases and, accordingly, apoptosis of cholangiocytes.

Phosphatidylcholine, as a component of essential phospholipids (EPL), also has an antifibrotic effect, contributing to its regression by suppressing collagenase activity and transforming stellate cells into collagen-producing ones, which is complemented by an anti-inflammatory effect by reducing the synthesis of pro-inflammatory cytokines (TNF- α , IL-1b).

Glycyrrhizic acid (GA) as a drug acting on specific mechanisms of fibrogenesis was studied as early as the beginning of the 20th century. Japanese scientists as a potential antifibrotic drug. Histological and biochemical studies have shown that GA administration restores the functional

activity of liver cells (K. Fakahashi, 1982), normalizes the enzyme spectrum of blood in patients with acute and chronic hepatitis. Glycyrrhizic acid complements the hepatoprotective effect of phospholipids, possessing high biological and detergent activity (Y. Kageuama et al., 1994). In addition, HA is a synergist of corticosteroids, and also has an antiallergic effect (O.Yu. Abakumova et al., 1996) (GA is an antagonist of acetylcholine, histamine and other inflammatory mediators). The main effects of GA, indirectly associated with anti-fibrotic action, included anti-inflammatory, when it inhibited histamine, serotonin, bradykinin, formalin and other inflammatory reactions, while reducing vascular permeability. In addition to the anti-inflammatory effect, GA has antioxidant activity, which is associated with an increase in lipid peroxidation through phosphorylation of 5-lipoxygenase. The action of the GC inhibits this process. In addition, GA is able to bind to a prooxidant, prostaglandin E2. Direct antifibrotic mechanisms of GA have been proven in an experimental model of rat LF induced by subcutaneous CCl4 injections. Using RT-PCR analysis (reverse transcription - polymerase chain reaction or RT-PCR analysis), an increase in the expression of genes (smurf2, PTAFR, CYP2D6, FGG) associated with inflammation was shown. Based on the data obtained, the anti-fibrotic effect of GA in animal models was proved, which was realized by the restoration of the activity of tissue metalloproteinases and a decrease in their inhibitors. This hypothesis has been confirmed in subsequent experimental and clinical studies. The administration of glycyrrhizin and glycyrrhizic acid suppresses the activation of the COL1A2 collagen gene promoter and the progression of LF caused by the repeated administration of carbon tetrachloride. Glycyrrhizic acid suppresses the synthesis of type 1 collagen at the level of gene transcription, and also inhibits the activation of HSCs, which regulate the balance between the processes of ECM synthesis and degradation. In the course of randomized trials, it was shown that, compared with placebo, taking glycyrrhizin leads to a significant decrease in the level of liver transferases and an improvement in the histological picture. This information about the short-term efficacy of these drugs was confirmed in a retrospective study, which showed that long-term use of glycyrrhizin prevents the development of LC and hepatocellular carcinoma in the presence of chronic hepatitis C.

When studying the effect of GA on the synthesis and proliferation of DNA in the primary culture of hepatocytes of adult rats, it was demonstrated that glycyrrhizin stimulates the phosphorylation of receptors for epidermal growth factor and p42 MAP-kinase, activates the synthesis of DNA of hepatocytes. In addition, HA inhibited tumor growth in mice due to an indirect antitumor effect. Thus, the protective effect of GA against carcinogen-induced DNA damage was shown, as well as the possibility of down-regulation of the epidermal growth factor receptor. Polyphenols (GA) contained in licorice induce apoptosis in cancer cells.

As promising areas of antifibrotic therapy, the experiment proved the clinical significance of prescribing growth factors (IGF, hepatocyte growth factor, cardiotropin) and factors that stimulate genes responsible for their production. Endothelin-1 receptor blockers type A and the administration of vasodilators (such as prostaglandin E2 and donor nitrogen nitrite) have shown good antifibrotic activity in rodents, but their effects have not been evaluated in humans.

An alternative approach to LF treatment is the use of collagen inhibitors and collagen degradation promoters. Thus, inhibitors of prolyl-4-hydroxylase and halofuginone prevent the development of experimental LC by inhibiting collagen synthesis. Factors such as MMP-8, plasminogen and urokinase activators stimulate collagen degradation in vivo. In an experiment with infusion of mesenchymal stem cells, a decrease in induced fibrosis was obtained, which could potentially be used in the future in the treatment of chronic liver diseases [28]. In general, the development of pathways for influencing activated HSCs can help resolve problems associated with the formation and progression of fibrosis. Thus, promising preliminary results were obtained using various carriers (cyclic peptides in combination with albumin-recognizing collagen receptors type 4 and / or PDGFR). Large-scale clinical trials are needed to confirm these data.

Currently, a sufficient number of scientific studies have been carried out in which the importance of inhibition of the RAAS is confirmed as a factor affecting PH and decreasing the rate of progression of LF, which may become a promising strategy in the treatment of this condition. This fact is confirmed by the fact that this group of drugs as antifibrotic agents have entered the treatment standards and are widely used by patients with chronic heart and kidney diseases. According to the reports of the transplantation departments, patients after liver transplantation, taking RAAS inhibitors and antihypertensive drugs, have less pronounced progression of fibrosis than patients receiving other types of treatment. However, multicenter clinical trials have not yet been completed and the results have not been processed.

Pentoxifylline (phosphodiesterase inhibitor), amiloride (sodium hydrogen pump inhibitor), S-farnesylthiosalicylic acid (RAS antagonist) as substances that inhibit key signaling pathways of liver fibrogenesis are also of potential importance in the complex therapy of this condition. For specific forms of liver damage, in particular in non-alcoholic steatohepatitis, the effect on specific ligands, for example, on a decrease in the expression of the SREPB-1c gene and an increase in PPRA α activity, has a positive effect on LF regression mainly in patients with disorders of carbohydrate metabolism (S16). Treatment of portal hypertension in patients with LF should be started at the earliest stage, when the first portal circulation disorders appear. At the stage of initial PG, hemodynamic disorders occur mainly at the functional level with the development of disorders of the parasympathetic regulation of vascular tone and the predominance of sympathicotonia, the appearance of microcirculation disorders and the rheological properties of blood [29]. For the correction of the initial PH it is recommended to use β -blockers, antagonists of aldosterone and angiotensin receptors, pentoxifylline, antioxidants. In essence, a real and universal regimen of antifibrotic therapy, especially for patients with advanced fibrosis and hepatic hypertension, today are: a combination of oral and parenteral forms of essential phospholipids (5.0 intravenously, 3-5 times a week); UDCA at a dose of 15–20 mg / kg / day; propranolol 40–80 mg / day. An indicator of the effectiveness and sufficiency of the dose of the drug is a decrease in heart rate by 25% compared to the initial one. The duration of courses of admission is determined individually from 1 to 6 months with a repeated course in 1-6 months; veroshpiron at a neurohormonal modulator dose of 12.5–25.0 mg / day with a duration similar to anaprilin; tocopherol (100–150 mg / day) for up to 4–8 weeks; trental (2% - 5 ml intravenous drip) and rheopolyglucin (400 ml). Treatment should be carried out in courses of up to 5-10 procedures. Thus, complex therapy of fibrosis and a decrease in the rate of its progression in chronic liver diseases remain a complex, filigree, but vital task in order to prevent fatal multiple organ disorders.

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