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Current strategies for targeted therapy of liver fibrosis

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ABSTRACT

Liver fibrosis (LF) is an unfavorable event in the natural course of chronic liver diseases (CLD), therefore, early implementation and widespread use of antifibrotic therapy methods is a pressing issue in hepatology. The aim of the review was to describe current approaches to targeted therapy of LF.

PubMed database, Google Scholar search engine, Cochrane Database of Systematic Reviews, eLIBRARY.RU scientific electronic library, as well as reference lists of articles were used to search for scientific articles. The publications that corresponded to the aim of the study were selected for the period from 1998 to 2021 by the terms "liver fibrosis", "pathogenesis", and "treatment". Inclusion criteria were restricted to targeted therapy of LF.

Despite the growing evidence for reversibility of LF, there are currently no effective or clinically approved regimens for its specific therapy. However, taking into account the relevance of the issue, scientific research in this area is necessary. Multiple drugs with a good safety profile have been studied, which, though intended for other purposes, can have a positive effect on LF. In addition, a number of innovative approaches that differ from pharmacotherapy inspire optimism about finding a solution to this problem. It is obvious that studies focused on well-characterized groups of patients with confirmed histologic, elastography, clinical, and radiological parameters are required. This is a challenging task, since the key point will be stratification of risk based on ethnicity, etiology, and clinical status, and very large samples will be required for a reliable assessment. Nevertheless, the solution will increase efficiency of treatment for patients with CLD, improve their prognosis and quality of life, and significantly reduce the need for liver transplantation, a demand for which remains extremely high worldwide.

Keywords: overview, liver fibrosis, pathogenesis, treatment

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Современные стратегии таргетной терапии фиброза печени

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РЕЗЮМЕ

Учитывая, что фиброз печени (ФП) является неблагоприятным событием естественного течения хронических заболеваний печени (ХЗП), скорейшее внедрение и широкое применение методов антифибротической

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терапии являются актуальной проблемой гепатологии. Цель обзора – описать современные подходы к таргетной терапии ФП.

Для поиска научных статей применялись база данных PubMed, поисковая система Google Scholar, Кокрановские систематические обзоры, научная электронная библиотека eLIBRARY.RU, а также пристатейные списки литературы. Соответствующие цели обзора публикации отбирались за период с 1998 по 2021 г. по терминам «фиброз печени», «патогенез», «лечение». Критерии включения ограничивались таргетной терапией ФП.

Несмотря на растущее число доказательств обратимости ФП, в настоящее время пока не существует каких-либо эффективных или одобренных для клинического применения схем его специфической терапии. Однако, принимая во внимание актуальность вопроса, научные поиски в этом направлении необходимы. Были изучены многочисленные лекарственные средства с хорошим профилем безопасности, которые хотя и предлагались для других целей, способны оказывать позитивное влияние на ФП. Кроме того, ряд отличных от фармакотерапии новаторских подходов вселяют оптимизм относительно успешности решения данной проблемы. Очевидно, что необходимы исследования, сосредоточенные на хорошо охарактеризованных группах пациентов с подтвержденными гистологическими, эластографическими, клиническими и радиологическими показателями. Это достаточно сложная задача, поскольку ключевым моментом будет стратификация риска на основе этнической принадлежности, этиологии и клинического статуса и для достоверной оценки потребуются очень большие размеры выборок. Тем не менее ее решение позволит повысить эффективность лечения пациентов с ХЗП, улучшит прогноз и качество их жизни, а также существенно уменьшит необходимость в трансплантации печени, потребность в которой во всем мире остается чрезвычайно высокой.

Ключевые слова: обзор, фиброз печени, патогенез, лечение

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INTRODUCTION

Chronic liver diseases (CLD) cause more than two million deaths worldwide annually, which, taking into account the heavy burden of CLD-related disability and seeking medical care, makes the problem extremely urgent. The most common causes of CLD are HBV and HCV, alcohol abuse, and metabolic disorders. The key step in their natural course is liver fibrosis (LF), which is considered as an abnormal wound-healing response to chronic liver injury. Diffuse excessive deposition and abnormal distribution of the extracellular matrix (ECM) further leads to the development of liver cirrhosis (LC). The severity of clinical manifestations of LC is primarily associated with liver failure and portal hypertension, as well as the occurrence of complications characteristic of them, accompanied by high mortality [1].

The growing evidence of the reversibility of LF, the identification of the main causes and mediators of its progression, as well as advances in non-invasive assessment of this pathological process contributed to treatment development. In general, there is no effective or clinically approved specific therapy of LF yet. Nevertheless, taking into account the relevance of the problem, there is a need for scientific research devoted to it. Of course, these studies should comply with the recommendations adopted in 2014 with the support of the American Association for the Study of Liver Diseases (AASLD) at the conference focused on clinical trials on antifibrotic therapy for CLD aimed at identifying potential unpredictable consequences and / or adverse outcomes associated with antifibrotic therapy in CLD patients [2].

Given that, numerous drugs with a good safety profile were studied, which were offered for other purposes, but had a positive effect on LF. In addition, a number of innovative approaches other than pharmacotherapy are promising when it comes to resolving the issue discussed.

Currently, it has been established that treatment of diseases, the natural course of which is accompa-

nied by LF, is an effective way not only to prevent LF, but also to reverse histologic diseases and restore the structure and function of the liver [3]. In addition, the following strategies of targeted therapy for LF can be distinguished:

– to affect hepatic fibrogenesis and decrease ECM synthesis:

– reduction of inflammatory and immune response;

to affect ligand binding to the receptor and intracellular signaling;

– induction of apoptosis, deactivation and immune clearance of activated hepatic stellate cells (HSCs);

– direct inhibition of collagen synthesis;

2) stimulation of liver regeneration and initiation of LF regression:

– activation of ECM degradation;

– mesenchymal stem cell (MSC) transplantation [4].

STRATEGIES TO AFFECT HEPATIC FIBROGENESIS AND DECREASE EXTRACELLULAR MATRIX SYNTHESIS

Reduction of inflammatory and immune response

The inflammatory response promotes the transition of HSCs from a quiescent to an activated and proliferative state, which causes ECM deposition and at the same time disrupts the immune function of the liver, which aggravates damage to hepatocytes. Therefore, suppression of the inflammatory and immune response is an important approach in the treatment of LF.

Transforming growth factor (TGF)-β is the main profibrogenic cytokine, with the participation of which quiescent HSCs transdifferentiate into myofibroblasts, directly involved in the ECM formation. Therefore, it seems obvious that the suppression of its overexpression and activity may be a promising goal of antifibrotic therapy [5]. For example, J. George et al. [6] reported that the antagonist of the TGF-β receptor ("soluble receptor"), which consists of the extracellular domain of the TGF-β receptor type II (TßRII) fused with chimeric IgG, is an effective inhibitor of experimental hepatic fibrogenesis in rats.

It was shown that the serine protease inhibitor *camostat mesilate* inhibited the production of TGF-β and blocked the HSC activation *in vitro*. In the *in vivo* model, camostat mesilate (1–2 mg / g of diet) markedly attenuated an increase in hepatic plasmin and TGF-β levels, HSC activation, and LF without apparent systemic or local side effects [7].

The chemopreventive drug against carcinogenesis *oltipraz* in an animal experiment inactivated HSCs and suppressed the expression of TGF-β1 [8]. In a randomized, double-blind, placebo-controlled phase II trial involving 83 patients with LF / LC who received oltipraz 60 mg BID, the area of collagen deposition in the liver and plasma TGF-β1 levels tended to decrease by week 24 [9].

Tenofovir is one of the first-line therapies in decompensated HBV-associated LC, as it demonstrated efficacy in preventing progression and reversing CCl4-induced LF in mice through assembling TGF-β1 / SMAD3 and NF-kB / NLRP3 inflammasome signaling pathways through upregulating the expression of NS5ATP9. Tenofovir also regulates the differentiation, activation, and proliferation of HSCs [10].

Numerous animal studies have demonstrated that the activation of platelets, which are a source of profibrogenic cytokines and growth factors, such as TGF-β1, platelet-derived growth factor (PDGF), and epidermal growth factor (EGF), contributes to the development and progression of LF [11]. At the same time, *antiplatelet agents* demonstrate opposite effects, which was confirmed in a systematic review and meta-analysis of four studies with a total population of 3,141 patients [12].

A soluble β-galactoside-binding protein *galectin-3* performs numerous autocrine and paracrine functions. It activates neutrophils, labrocytes, and T lymphocytes, regulates cell adhesion, and induces apoptosis and angiogenesis. Depending on the cell type and the balance between extracellular and intracellular content, galectin-3 can both inhibit and induce cell growth and differentiation. Galectin-3 is crucial for protecting the body from pathogens. It enhances proinflammatory signals, and its monocyte / macrophage chemotaxis contributes to neutrophil adhesion, the release of proinflammatory factors, namely leukocytes and labrocytes. In addition, galectin-3 induces phagocytosis. In preclinical studies on rats, it was noted that GR-MD-02, a galectin-3 inhibitor, reduces collagen deposition and leads to regression of LF and reversal of LC [13]. The first randomized phase I clinical trial, which involved patients with non-alcoholic steatohepatitis (NASH) confirmed by the histologic examination, and extensive LF, demonstrated its safety and good tolerability [14].

Emricasan (IDN-6556), an orally active, irreversible pan caspase inhibitor, was found to reduce hepatocyte apoptosis, inflammation, and LF in CCl4-induced cirrhosis model in rats. It also decreased high

caspase activity and serum alanine aminotransferase (ALT) levels in patients with chronic hepatitis C and non-alcoholic fatty liver disease (NAFLD). Its effect on liver function was studied in a multicenter randomized controlled trial (RCT) including 86 patients with LC (Child–Pugh class A or B, mean score of 6.9; 38% with alcohol-associated LC, 29% with HCV-associated LC, and 23% with NASH; and the Model for End-stage Liver Disease (MELD) score of 11–18 (mean score of 12.8)).

Patients were randomly divided into groups receiving placebo (n = 42) or emricasan (25 mg, n = 44) BID for 3 months. Then the subjects received emricasan (25 mg) BID for 3 months in the open-label second stage. At the 3-month timepoint, emricasan significantly reduced the mean MELD (p = 0.003) and Child–Pugh (p = 0.003) scores in subjects with high MELD scores (15 or more), compared with placebo, with significant reductions in international normalized ratio (INR) (95% confidence interval (CI) from –0.2882 to –0.0866) and total bilirubin (95% CI, from –1.5069 to –0.0823) as opposed to placebo. There were no significant differences between emricasan and placebo groups in the mean MELD (p = 0.466) or Child–Pugh (p = 0.124) scores at 3 months compared with placebo. Serum levels of full-length cytokeratin (CK)-18 (p = 0.02) and caspase (p < 0.001), but not caspase-cleaved CK-18 (p = 0.092), decreased significantly at 3 months in the emricasan group as opposed to the placebo group. Emricasan was well tolerated, and adverse events were balanced between the groups [15].

Other results were obtained in a double-blind, randomized, placebo-controlled trial in which taking emricasan (5 mg / day for an average of 43 weeks or 25 mg / day for an average of 42 weeks) did not reduce the number of cases of decompensation or did not improve liver function in patients with NASH-related decompensated LC (n = 217) [16].

In vitro and *in vivo* models showed a positive effect on liver function and LF of the Chinese herbal medicine, *Gan Shen Fu Fang* (GSFF) consisting of salvianolic acid B and diammonium glycyrrhizinate. GSFF alleviated inflammatory cell infiltration and reduced synthesis of proinflammatory cytokines (tumor necrosis factor α (TNFα) and interleukin (IL)-1β) and NF-kB, as well as ERK phosphorylation in rats with common bile duct ligation after 3 weeks of treatment. *In vitro*, GSFF inhibited viability of HSC-T6 cells and expression of alpha-smooth muscle actin (α-SMA) in them and decreased synthesis of collagen I [17].

By attenuating the effects of reactive oxygen species (ROS) and preventing damage to hepatocytes, antioxidants can be potential antifibrotic agents provided they are directly delivered to the pathological focus [18].

In particular, *S-adenosyl-L-methionine* has shown the ability to reduce ROS and inhibit the HSC activation both in rats with the LF model [19] and in clinical trials. In a long-term, multicenter, double-blind, randomized, placebo-controlled clinical trial in patients with alcoholic LC, it improved survival and delayed the need for liver transplantation [20]. The suppression of ROS and NADPH oxidase 4, which are induced by TGF-β1, is a possible therapeutic target of *polyene phosphatidylcholine* to attenuate HSC activation. However, its effectiveness in patients with alcohol-related liver disease when taken for two years was insignificant [21].

Although *vitamin E* is a prototype of an antioxidant and can induce a strong anti-NASH effect, in a large RCT by A.J. Sanyal et al. [22], it did not have a positive effect on the severity of LF. *Naringenin* is a flavonoid with antioxidant, antifibrogenic, anti-inflammatory and anticancer properties that is capable of preventing liver damage caused by different agents. The main protective effects of naringenin in liver diseases are inhibition of oxidative stress and TGF-β pathway and prevention of HSC transdifferentiation, leading to decreased collagen synthesis. Other effects include inhibition of the mitogen activated protein kinase (MAPK), toll-like receptor (TLR), and non-canonical TGF-β pathways, which further results in drastic reduction of ECM synthesis and deposition. In addition, naringenin demonstrated a beneficial effect on NAFLD by regulating lipid metabolism and modulating synthesis and oxidation of lipids and cholesterol. It is safe, but has low bioavailability and high intestinal metabolism [23].

The use of anti-inflammatory drugs, in particular, *corticosteroids*, as a part of antifibrotic therapy is justified [24]. However, the suppression of hepatic fibrogenesis caused by them is incomplete, which does not prevent the development of LF [25]. Another pathogenetic strategy is neutralization of proinflammatory cytokines, for example, TNFα, by exposure to compounds directed against it, such as *infliximab*, *etanercept,* and *pentoxifylline* [26].

Effect on ligand binding to the receptor and intracellular signaling

Identification of the membrane and nuclear receptors expressed by HSCs revealed new targets for antifibrotic therapy, which include the renin – angiotensin

system, neurotransmitters, endothelin-1 and their receptors, receptor tyrosine kinases, etc., as well as intracellular signaling involving nuclear receptors, such as PPARs, FXR, PXR, LXR, etc. [27].

It is known that angiotensin II is the key mediator of hepatic fibrosis. Its synthesis by HSCs increases as a result of overexpression of angiotensin-converting enzyme [28]. Oral administration of the angiotensin II inhibitor *losartan* (50 mg / day) for 18 months in patients with chronic hepatitis C was associated with a significant decrease in the expression of NADPH oxidase, several profibrogenic type I collagen genes, matrix metalloproteinase (MMP)-2, and urokinase [29]. In a retrospective study, K.E. Corey et al. [30] also found a beneficial role of angiotensin II blockade in hepatitis C virus-related fibrosis [30].

Resolution of NASH as a result of blockade of important inflammation and LF triggers and chemokine receptors CCR2 / CCR5 by their antagonist *cenicriviroc* was described [31].

In recent years, a number of multitargeted inhibitors of the aberrant activity of receptor and non-receptor tyrosine kinase, including sorafenib, erlotinib, imatinib, sunitinib, nilotinib, brivanib, and vatalanib, were investigated as potential drugs for the treatment of LF. Among them, *sorafenib* is the most studied one, which is the first systemic drug that has demonstrated a positive effect on survival in advanced hepatocellular carcinoma [32]. In animals with different models of LC, it also affected some pathogenetic pathways of liver fibrogenesis and angiogenesis by blocking the receptor tyrosine kinases located on the surface of HSCs, the expression of which, especially VEGFR and PDGFR, was increased. As studies revealed, the positive effects of sorafenib were due to:

– the suppression of activated HSC proliferation and the activation of apoptosis;

– the inhibition of cyclin D1 and cyclin-dependent kinase 4 (Cdk-4) with a simultaneous increase in the expression of Fas, Fas-L, and Caspase-3, and a decrease in the Bax / Bcl-2 ratio;

– an increase in the MMPs / tissue inhibitor of matrix metalloproteinases (TIMPs) ratio, and also a decrease in the synthesis of collagen by HSCs;

– the inhibition of phosphorylation of ERK, Akt, and ribosomal protein kinase S6 with a molecular mass of 70 kDa (p70S6K);

– the disturbance of the molecular triad functioning: Kruppel-like factor 6 – angiopoietin 1 – fibronectin [33].

The number of PPARγ located in the HSCs decreases during their activation and progression of LF, whereas stimulation of PPARγ overexpression leads to reduction of collagen production and an increase in metalloproteinase activity of HSCs. Synthetic ligands of PPARγ thiazolidinediones, including *pioglitazone* and *rosiglitazone*, well studied in patients with NASH, showed a positive effect on steatosis, necroinflammation, hepatocyte ballooning, and LF, although in the long term it may be offset by side effects [34].

Animal experiments showed that the transrepressive activity of PPARα in hepatocytes in NASH prevents the progression of steatosis and LF due to the effect on lipid metabolism-related genes [35]. Although the use of *fenofibrate*, a PPARα agonist, in patients with NAFLD at a dose of 200 mg / day for 48 weeks is safe and improves metabolic syndrome, serum glucose levels, and liver tests, its effects on liver histology are minimal [36].

Preliminary data on PPARα/γ agonists (*glitazars*) revealed their positive effect on the lipid profile, blood pressure, atherosclerosis, and inflammation. Overexpression of PPARβ/δ prevented obesity and reduced lipid stores in cardiac cells, and stimulation of PPARα/δ with *elafibranor* caused the resolution of NASH without LF aggravation [37]. The pan-PPAR agonist (α/γ/δ) *lanifibranor* in preclinical models of decompensated LC contributed to a decrease in the severity of LF and portal hypertension [38].

An interim analysis within a multicenter, randomized, placebo-controlled phase III (REGENERATE) trial showed clinically significant histologic improvement in patients with NASH following inhibition of the HSC activation by the FXR nuclear receptor agonist *obeticholic acid* [39]. Another FXR agonist *tropifexor* in the experiment on mice contributed to the regression of the formed LF and reduced the NAFLD fibrosis score (NAS) parameters, the level of triglycerides in the liver, and the expression of profibrogenic genes [40]. Currently, clinical trials are being conducted to assess the safety, tolerability, and efficacy of various doses of this drug in patients with NASH [41].

A powerful FXR agonist EDP-305 in mice with LF models showed significant histologic improvement; in particular, it reduced the deposition of collagen in the liver [42]. In rats with the NASH model, the combined use of the FXR agonist 1INT747 and the angiotensin II inhibitor losartan suppressed hepatic fibrogenesis, reversing intestinal barrier dysfunction and inhibiting the proliferation of activated HSCs [43].

The role of LXR nuclear receptor, which is the key regulator of lipogenesis and modulator of the immune system, in hepatic fibrogenesis is still being investigated. S.W. Beaven et al. [44] in *in vitro* and *in viv*o experiments demonstrated that LXR ligands suppress HSC activation and the expression of fibrogenic genes. In addition, Lxrαβ (-/-) mice showed hypersecretion of inflammatory mediators and increased susceptibility to LF. Nevertheless, to date, researchers express doubts regarding the expediency of using LXR agonists as potential antifibrotic agents due to hepatotoxicity and induction of *de novo* lipogenesis [45].

Induction of apoptosis, deactivation, and immune clearance of activated HSCs

Apoptosis of activated HSCs and their deactivation or direct reduction of their number by immune clearance are currently considered as an important approach in the treatment of LF. It has been established that drug-induced apoptosis of activated HSCs can be achieved as a result of NF-kB inhibition using *fraxetin* (7,8-dihydroxy-6-methoxycoumarin) [46] and 4-hydroxy-2(3H)-benzoxazolone [47]; modulation of alternative splicing of Bcl-x by antisense oligonucleotides [48] and selective STAT1-dependent induction by the synthetic antiviral drug *rilpivirine*, which can also cause STAT3-dependent proliferation of hepatocytes and liver regeneration [49].

In vivo and *in vitro* models showed that *selonsertib*, a selective ASK1 kinase inhibitor with low molecular weight, suppressed HSC activation and reduced collagen production, induction of inflammatory cytokine pathways, and oxidative stress [50]. At the same time, subsequent phase II and III clinical trials did not reveal convincing data regarding its positive effect on LF in patients with NASH [51, 52].

As an important part of innate immunity, invariant natural killer T (iNKT) cells can kill activated HSCs. However, highly activated peripheral iNKT cells also cause MIHAcell line proliferation and HSC line (LX-2) activation through the expression of IL-4 or IL-13, which contributes to the progression of LF [53]. Thus, understanding the iNKT balance in the regulation of HSCs in patients with CLD can help in the development of new antifibrotic drugs.

Curcumin, the major natural polyphenol isolated from the rhizome of *Curcuma longa,* is a well-known hepatoprotector. In an experiment on rats, it decreased CCL4-induced liver damage, oxidative stress, fibrosis, and restored the activity of MMP-9 and MMP-2. Besides, curcumin restored the levels of NF-kB, IL-1, IL-10, TGF-β, connective tissue growth factor (CTGF), type I collagen, MMP-13, and Smad7. It also reduced JNK and Smad3 phosphorylation and the levels of protein and α-SMA and SMAD3. Curcumin normalized GSH and NF-kB, as well as JNK-Smad3 and TGF-β-Smad3 pathways, leading to reduction of the number of activated HSCs and contributing to the antifibrotic effect [54].

In a randomized, double-blind, placebo-controlled trial, 70 patients with LC were randomly divided into two groups: group 1 received 1,000 mg / day curcumin (n = 35), group 2 received placebo (n = 35) for 3 months. At the final stage, the patients receiving curcumin (n = 29) showed a decrease in the MELD (i) (from 15.55 ± 3.78 to 12.41 ± 3.07; $p < 0.001$), MELD (from 15.31 ± 3.07 to 12.03 ± 2.79; $p < 0.001$), MELD-Na score (from 15.97 ± 4.02 to 13.55 ± 3.51; $p = 0.001$), and Child – Pugh score (from 7.17 ± 1.54 to 6.72 ± 1.31; $p = 0.051$). At the same time, in the placebo group (n = 31), these parameters increased significantly ($p < 0.001$ in all cases) [55].

Direct inhibition of collagen synthesis

Another promising strategy for the treatment of LF is to directly affect collagen synthesis. For example, in a multicenter, open-label PROMETEO study involving 281 patients with CLD of various etiology and advanced LF, the safety and efficacy of 12-month use of *pirfenidone*, an immunosuppressant (600 mg orally, every 12 h), in combination with standard treatment was studied. The results showed that 35% of the patients who received it had a significant decrease in the severity of LF. The Child – Pugh score improved in 29.7% of cases. Serum ALT and aspartate aminotransferase (AST) decreased by 40.6% and 43.3%, respectively. In addition, the patients receiving the immunosuppressant showed lower serum levels of TGF-β1 than those treated only according to the standard scheme [56].

Colchicine is a plant alkaloid that inhibits polymerization of microtubules and, thereby, prevents collagen secretion. In the RCT involving 38 patients, the effect of colchicine on LF of various etiologies was studied. Patients included in group A (n = 21) were prescribed the drug at a dose of 1 mg per day. Those who did not receive it made up group B (n = 17). After 12 months, the average serum albumin levels increased only in group A ($p < 0.05$). After 12 months of the treatment in group A, the average serum values of PIINP, a biomarker of LF, did not change significantly and decreased in 7 patients after 24 months ($p < 0.05$).

No significant histologic changes on the Knodell score were found in both groups after 12 months of follow-up [57].

The efficacy and safety of colchicine was evaluated in the Cochrane meta-analysis combining the results of 14 RCTs and including a total of 1,150 patients with LF of alcoholic, viral, and unidentified etiology. There was no significant effect of colchicine on the all-cause mortality (odds ratio (OR) 0.90, 95% confidence interval (CI): 0.63–1.29), liver-related mortality (OR 1.05, 95% CI: 0.61–1.80), complications (OR 1.01, 95% CI: 0.63–1.62), and hepatic biochemical and histologic parameters (OR 1.02, 95% CI: 0.58–1.79). In addition, its administration was accompanied by an increased risk of adverse events (OR 4.92, 95% CI: 2.66–9.10; $p < 0.001$) [58].

STIMULATION OF LIVER REGENERATION AND INITIATION OF LIVER FIBROSIS REGRESSION

Activation of extracellular matrix degradation

Given that MMPs and TIMPs are crucial for the development of LF, and the balance between them is important for the homeostasis of ECM components, it is expected that they will become new therapeutic targets in the treatment of CLD [59]. An increase in the activity of enzymes that destroy ECM, as well as their introduction by gene therapy, can enhance the degradation of ECM. For example, in experiments on rats with different LC models, the attenuation of LF was associated with increased regulation of MMP-1 and MMP-8 caused by transfection of their genes [60].

An experimental study by O. Ohayon et al. [61] demonstrated that treating fibrotic rat livers with *halofuginone*, a multipotent antifibrogenic drug, and subsequently subjecting them to hydrodynamics-based transfection with human VEGF-165 resulted in elevated expression of heparan sulfate-degrading heparanase. Moreover, these rats demonstrated an improved capacity to regenerate following partial 70 % hepatectomy. *In vitro*, halofuginone stimulated heparanase and vascular endothelial growth factor (VEGF) expression in HSCs.

An experiment on mice showed the ability of *polaprezinc* to attenuate LF at the late stages of NASH by inhibiting the expression of TIMPs [62]. Lysyl oxidase like-2 (LOXL2) mediates type I collagen crosslinking and ECM stabilization during hepatic fibrogenesis, and also independently promotes differentiation of fibrogenic hepatic progenitor cells. *In vitro* and *in vivo* models demonstrated that the blockade of these two convergent profibrotic pathways by therapeutic inhibition of LOXL2 with the monoclonal antibody AB0023 attenuates LF and leads to its regression [63].

An open-label, pilot phase II clinical trial studied the safety and tolerability of *simtuzumab*, a monoclonal antibody directed against LOXL2, in subjects with advanced CLD, caused by HCV, human immunodeficiency virus (HIV), or HCV – HIV coinfection. The drug was administered at a dose of 700 mg intravenously every 2 weeks for 22 weeks. The treatment was well tolerated, but there were no significant changes in the severity of morphological signs of LF, as well as values of the hepatic venous pressure gradient [64].

It was established that an immunosuppressant *pirfenidone* can successfully reduce the expression of HSP47 protein and, by regulating the activity of the TGF-β signaling pathway, inhibit HSC proliferation, reduce the abnormal accumulation of type I and type III collagen, as well as suppress the expression of type II collagen, TIMP-1, and MMP-2. Its efficacy was studied in 28 patients with chronic HCV who received pirfenidone (1,200 mg / day) for 24 months. Six patients dropped out after 12 months of the therapy. At the end of the treatment, necroinflammation grades were reduced by an average of 3.2 points in 82% of patients ($p < 0.05$) and Ishak fibrosis score decreased by an average of 2 points in 67% of patients ($p < 0.05$). Liver steatosis decreased in 61% of patients. Serum IL-6 and TGF-β1 levels decreased significantly in 93% and 67% of patients ($p < 0.05$), respectively, while TNF-α decreased in 47% of patients. Serum ALT and AST levels tended to normalize in 81% of patients. The levels of mRNA of antifibrogenic cannabinoid receptors CB2 in the liver increased in 86% of cases, and the expression of receptors CB1 decreased in 29% of patients. Improvements in the quality of life and the Child – Pugh score were reported in all patients [65]. Despite the promising results, there are still concerns about the potential side effects and adverse events associated with pirfenidone [66].

Mesenchymal stem cell transplantation

Mesenchymal stem cell (MSC) transplantation is an important and promising approach in the treatment of LF. These multipotent fibroblast-like cells are characterized by the expression of CD73, CD90, and CD105 surface antigens, the absence of expression of CD45, CD34, CD14, Cd11b, CD19, CD79a, and HLA-DR, adhesion to plastic, and the ability to differentiate into osteoclasts, chondrocytes, adipocytes,

and hepatocytes. The largest source of MSCs is bone marrow. In addition, they can be obtained from adipose tissue, umbilical cord tissue, amniotic fluid, breast milk, synovial membrane, placental cells, tooth pulp, lungs, and liver (in both adults and fetus).

In addition to the immunomodulatory effect on T cells, B cells, and macrophages, MSCs have antifibrotic effects both through immunomodulation and by direct inhibition of the proliferation of activated HSCs, increasing the activity of MMPs and suppressing the synthesis of ECM [67]. They also contribute to an increase in proliferation and reduction of hepatocyte apoptosis and elevated expression of certain anti-inflammatory and antifibrotic cytokines with potential hepatotropic properties, including hepatocyte growth factor (HGF), VEGF, basic fibroblast growth factor (bFGF), placental growth factor (PlGF), monocyte chemoattractant protein (MCP)-1, stem cell factor (SCF)-1, chemokine SDF-1, CD135 or FMS-like tyrosine kinase 3 (FLT-3), granulocyte-macrophage colony-stimulating factor (GM-CSF), and numerous ILs [68]. In addition, the MSCs-stimulated proliferation of hepatocytes from an increased population of hepatic progenitor cells leads not only to a decrease in the severity of LF, but also to liver regeneration [69].

MSCs are chosen for transplantation due to their availability and low immunogenicity. In addition, researchers using MSCs face fewer ethical problems due to their non-somatic origin, and the procedure is considered safe and was highly evaluated in clinical settings for various diseases, showing promising results [70]. The therapeutic efficacy of MSCs is affected by many factors, namely the cultivation method, strategy, and delivery routes. 3D cell culture is considered the most suitable and physiologically similar microenvironment for cell growth. There are many methods of 3D cell culture for the formation of MSC spheroids, such as hanging drop, magnetic cell levitation, chitosan membranes, microgravity bioreactor, and spinner flask [71].

In CLD, both direct (portal vein, hepatic artery) and indirect delivery routes of MSCs can be used, for example, intrasplenic, intraperitoneal, through peripheral veins, as well as through an extracorporeal liver support system. It is obvious that direct delivery provides a higher retention rate [72]. However, in patients with decompensated LC, it may be associated with an increased risk of bleeding associated with portal hypertension [73].

Preliminary experimental data are promising regarding the prospects of this method in the treatment of LF, while the results of clinical trials still require further evaluation [67]. For example, in a prospective study involving 90 patients with decompensated LC, bone marrow MSCs were transplanted simultaneously into the portal and peripheral veins (ratio 1 : 1) after 2 weeks, which led to a statistically significant improvement in serum levels of albumin, bilirubin, and INR. This effect persisted for 6 months in the patients who underwent one procedure and for 12 months in those who underwent a second procedure four months after the first one. By the end of the study, 36.7% and 66.7% of patients, respectively, had a decrease in ascites. In addition, there was an improvement in the hepatic functional reserve according to the Child – Pugh and MELD scores. The safety of the procedure was indicated by a low complication rate [74].

In a multicenter, randomized, open-label, phase II trial involving 72 patients with biopsy-confirmed alcoholic LC, single or double injections of 5×10^7 bone marrow MSCs into the hepatic artery after 6 months were associated with a 25% and 37% decrease in the proportion of collagen ($p < 0.001$), respectively, and an improvement in liver function parameters according to the Child – Pugh scores ($p < 0.05$) [75].

A RCT including 40 patients with HCV-induced decompensated LC showed that normalization of serum enzymes and improvement of liver protein synthesis were observed in 54 % of cases after infusion of bone marrow MSCs through peripheral veins. Three months after the transplantation, the values of serum PIIICP and PIIINP LF biomarkers decreased from 9.4 ± 4.2 to 8.1 ± 2.6 and from 440 ± 189 to 388 ± 102, respectively ($p = 0.7$) [76].

On the contrary, in a RCT involving 27 patients with decompensated LC, absolute changes in the Child – Pugh and MELD scores, serum levels of albumin, aminotransferases, and INR in patients who underwent infusion of bone marrow MSCs through peripheral veins and received placebo after 12 months of follow-up did not differ significantly [77].

CONCLUSION

Despite the relevance of the problem, it should be noted that before considering antifibrotic therapy as a gold standard of treatment for diseases which are accompanied by LF, studies should be conducted with a focus on well-characterized groups of patients with confirmed histologic, elastography, clinical, and radiological data. The above-mentioned is quite a difficult task, since the key point will be stratification of risk based on ethnicity, etiology, and clinical status, and

very large sample sizes will be required for a reliable evaluation. Nevertheless, the solution to the problem will increase the effectiveness of treatment in patients with CLD, improve their prognosis and quality of life, and significantly reduce the need for liver transplantation, which remains extremely high worldwide.

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