



Contemporary concepts of the medical therapy of portal hypertension under liver cirrhosis

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Abstract

Severe complications of liver cirrhosis are mostly related to portal hypertension. At the base of the pathogenesis of portal hypertension is the increase in hepatic vascular resistance to portal blood flow with subsequent development of hyperdynamic circulation, which, despite of the formation of collateral circulation, promotes progression of portal hypertension. An important role in its pathogenesis is played by the

rearrangement of vascular bed and angiogenesis. As a result, strategic directions of the therapy of portal hypertension under liver cirrhosis include selectively decreasing hepatic vascular resistance with preserving or increasing portal blood flow, and correcting hyperdynamic circulation and pathological angiogenesis, while striving to reduce the hepatic venous pressure gradient to less than 12 mmHg or 20% of the baseline. Over the last years, substantial progress in understanding the pathophysiological mechanisms of hemodynamic disorders under liver cirrhosis has resulted in the development of new drugs for their correction. Although the majority of them have so far been investigated only in animal experiments, as well as at the molecular and cellular level, it might be expected that the introduction of the new methods in clinical practice will increase the efficacy of the conservative approach to the prophylaxis and treatment of portal hypertension complications. The purpose of the review is to describe the known methods of portal hypertension pharmacotherapy and discuss the drugs that may affect the basic pathogenetic mechanisms of its development.

Key words: Liver cirrhosis; Portal hypertension; Pathogenesis; Medical therapy

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INTRODUCTION

Severe complications of liver cirrhosis are mostly related to portal hypertension. At the base of the pathogenesis of portal hypertension is the increase in hepatic vascular resistance to portal blood flow. It is now established that the reason for this, in addition to gross structural changes in the liver due to diffuse fibrosis and the formation of nodules of regenerating hepatocytes, remodeling and capillarization of the hepatic sinusoids, is endothelial dysfunction and the disorder of paracrine interactions between damaged hepatocytes, sinusoidal endothelial cells (SEC), Kupffer cells and activated hepatic stellate cells (HSC) of the liver^[1]. Further development of splanchnic hyperemia, the formation of collateral circulation and established hyperdynamic circulation, as a result of complex processes of angiogenesis, vascular remodeling and endothelial dysfunction, contributes to the progression of portal hypertension^[2]. It is obvious that the aim of pharmacotherapy should be to correct these disturbances, while striving to reduce the hepatic venous pressure gradient (HVPG) to less than 12 mmHg or 20% of the baseline. In addition, preventing arterial hypotension, it is necessary to reduce the inflow of splanchnic blood to the portal vein, while maintaining portal circulation, which participates in hepatic perfusion^[3].

Dissatisfaction with the existing methods of pharmacotherapy, as well as advances in understanding the pathogenesis of portal hypertension under liver cirrhosis, make finding effective drugs for the prevention and treatment of its complications a crucial task.

The purpose of the review is to describe the known methods of portal hypertension pharmacotherapy and discuss the drugs that may affect the basic pathogenetic mechanisms of its development.

CURRENT PHARMACOTHERAPY OF PORTAL HYPERTENSION

Most drugs used in clinical practice against portal hypertension are splanchnic vasoconstrictors, whose effect is based on reducing splanchnic blood flow and hyperdynamic circulation.

Vasopressin derivatives

Terlipressin (N-triglycer-8-lysine-vasopressin) is a synthetic analogue of vasopressin with a longer biological activity and a better safety profile, administered to liver cirrhosis patients with bleeding from esophageal varices and type I hepatorenal syndrome. The drug affects specific V1 receptors of smooth muscles of arteries. Its effects encompass a marked vasoconstriction of the splanchnic circulation, an increase in arterial blood pressure and systemic vascular resistance, and a decrease in cardiac output.

Møller *et al*^[4], having studied the influence of terlipressin on the hemodynamics in liver cirrhosis patients with portal hypertension, showed that an intravenous bolus of 2 mg of the drug leads to a fast reduction in portal pressure and hepatic blood flow (17% and 29%, respectively). It also increases blood pressure and systemic vascular resistance (26% and 61%, respectively), and reduced cardiac output, heart rate and elasticity of arteries (18%, 11% and 32%, respectively).

The effect of terlipressin lasts for up to 4 h, which allows administering it in periodic intravenous injection, but, if necessary, continuous infusion is also possible^[5].

In case of bleeding from esophageal varices in adults weighing over 40 kg, terlipressin is injected every 4 h, 2 mg in the first 1-2 d and 1 mg for 2-5 following days^[6]. Treatment of patients with type I hepatorenal syndrome starts with a 0.5-1 mg intravenous bolus every 4-6 h, or a continuous intravenous infusion at 2 mg/d. If the creatinine level is not reduced by more than 25% by the third day, the amount of drug injected by intravenous injection is increased to 2 mg every 4 h or to 12 mg/d with continuous infusion^[7].

The most frequent side effects associated with the use of terlipressin are moderate abdominal pain, arterial hypertension, hyponatremia; these generally have reverse development after its cancellation. Severe cardiovascular and ischemic disorders occur in about 15% of patients. In this regard, terlipressin is not recommended for patients with a history of ischemic heart or cerebral disease, limb or gut vascular disease, cardiomyopathy, bronchial asthma, chronic obstructive pulmonary disease, or having cardiac rhythm disturbance; caution should be used for elderly and/or hypertensive subjects^[8].

Somatostatin and long-acting somatostatin analogues

Somatostatin is a 14-amino-acid peptide secreted by neural, endocrine, and enteroendocrine cells in the hypothalamus and in the digestive system (in the stomach, intestine, and pancreatic delta cells of the pancreas). Somatostatin and its synthetic analogues (octreotide, vapreotide and others) are used in patients with liver cirrhosis for the treatment of bleeding from esophageal varices. It affects both intra- and extrahepatic mechanisms of portal hypertension.

Somatostatin reduces hepatic vascular resistance by blocking G-protein coupled receptors ET_A, which prevents the contraction of HSC induced by endothelin-1 (ET)-1 and contributes to the expansion of sinusoids. A similar effect of octreotide is associated with a decrease in intracellular Ca²⁺^[9]. With long-term use, the latter also positively influences hepatic fibrogenesis as a result of inhibiting the proliferative activity of HSC, decreasing the expression of the transforming growth factor β₁ (TGF-β₁), α-smooth muscle actin, intracellular

protein Smad4a and the suppression of transcription factors, in particular C-Jun and SP1^[10].

The reduction of portal inflow caused by somatostatin is explained by the weakening of splanchnic hyperemia due to somatostatin's antisecretory effect on the secretion of glucagon and other gastrointestinal vasodilating peptides. The positive effect of octreotide on splanchnic blood flow is due to both the potentiation of protein kinase of C-dependent vasoconstrictors through subtype 2 somatostatin receptors and the suppression of mesenteric angiogenesis at an early stage of portal hypertension^[11].

In patients with liver cirrhosis and portal hypertension an intravenous bolus of 250 µg of somatostatin contributes to a 28.4% reduction of wedged hepatic venous pressure and a 15%-71% reduction of the pressure in the esophageal varices. Continuous infusion of the drug reduces wedged hepatic venous pressure by 17% and hepatic blood flow by 17.4%. High doses of somatostatin (500 µg/h) have a more pronounced effect on these indicators, also reducing azygal blood flow by 45% in the case of bolus injection and by 23% with continuous infusion. A positive effect of the drugs in this group on the hemodynamics is short, despite the much larger half-life of synthetic analogues of somatostatin, compared with the natural hormone; this is probably due to the desensitization or tachyphylaxis^[12].

With bleeding from esophageal varices, 250 µg of somatostatin is initially injected as a bolus, and then in the form of continuous infusions, 250-500 µg/h for 2-5 d. The first dose of octreotide and vapreotide is 50 µg followed by an infusion of 50 µg/h. Severe complications in the course of this therapy are rare. Approximately 21% of patients may have vomiting and hyperglycemia, which, as a rule, can be easily remedied^[13].

Nonselective β-adrenergic blockers alone and combined with vasodilators

Nonselective β-adrenergic blockers, which are drugs of choice for the prevention of bleeding from esophageal varices^[14], affect several links of the pathogenesis of portal hypertension in cirrhotic patients: (1) blocking β₂-adrenergic vascular receptors, allowing unopposed α₁-adrenergic activity that results in splanchnic vasoconstriction and the reduction of portal inflow; (2) blocking β₁-adrenergic cardiac receptors reduces cardiac output, which improves the hyperdynamic circulation; (3) reduction of azygos blood flow and variceal pressure; and (4) shortening the intestinal transit time which has been related to decreased bacterial overgrowth and thereby reduced risk of bacterial translocation.

The first nonselective β-adrenergic blocker introduced into clinical practice for the treatment of portal hypertension was propranolol. Currently, its impact on portal and systemic hemodynamics is well studied.

It is established that it is able to decrease HVPG by 10%-31%, azygal blood flow by 29%-47%, cardiac output by 10%-31%, mean arterial pressure by 0%-14% and hepatic blood flow by 0%-39%^[15].

It is recommended to start the propranolol therapy with a dose of 20 mg/d, which can be increased, if necessary^[16]. However, one should be careful: Because of the possible negative reaction of systemic hemodynamics, there is a higher risk of severe complications and even deaths not related to variceal bleeding^[17]. In addition, it is still unclear whether patients with decompensated liver cirrhosis should take nonselective β-adrenergic blockers. In such patients, despite the increased volume of circulating blood, the effective arterial volume decreases, impairing the perfusion of vital organs, causing azotemia and creating a risk of hepatorenal syndrome^[18].

Clinical efficacy of nonselective β-adrenergic blockers against portal hypertension is variable. A number of studies have reported HVPG not decreasing by more than 20%, and the long term weakening of the therapeutic effect was observed in 50%-70% of patients^[19]. To improve the results of the treatment, it is possible to combine nonselective β-adrenergic blockers with drugs that reduce hepatic vascular resistance. Some of them are exogenous NO donors, nitrates; in particular, isosorbide-5-mononitrate, even lower doses which (10 mg/d) are able to blunt the postprandial increase in HVPG, not changing the perfusion of the liver^[20]. Although monotherapy of portal hypertension with nitrates in cirrhotic patients resistant to nonselective β-adrenergic blockers has been inconclusive, combining the medications proved to be effective^[21].

It was assumed that another combination could be the simultaneous use of nonselective β-adrenergic blockers and α₁-adrenergic blocker prazosin; not only can the latter reduce the HVPG, but also improve the perfusion of the liver. Indeed, their combined use has led to a greater reduction in portal pressure than the combination of propranolol with isosorbide-5-mononitrate. However, prazosin's lack of selectivity caused a significant decrease in arterial pressure and systemic vascular resistance, and induced stimulation of endogenous vasoactive systems led to increased plasma volume, the retention of sodium and water. Also, a potential drawback of long-term medication is the development of true tolerance associated with a decrease in the expression of α₁-adrenergic receptors in response to arterial hypotension^[22].

Carvedilol

In the past decade, there have been a number of reports about the use of the nonselective β-adrenergic blocker carvedilol to treat cirrhotic patients with portal hypertension. This drug has weak anti-α₁-adrenergic activity, which makes its effect similar to the

combination of propranolol and prazosin. It was found that carvedilol (12.5 mg/d) reduces HVPG significantly more than propranolol. Carvedilol is effective in 56% of patients resistant to propranolol, and surpasses it during primary prevention of bleeding from esophageal varices^[23]. However, in a systematic review and meta-analysis, Aguilar-Olivos *et al*^[24] showed limited evidence suggesting that carvedilol is more effective than propranolol for improving the haemodynamic response in cirrhotic patients with portal hypertension. Moreover, it had no advantages over the combination of nadolol and isosorbide-5-mononitrate used to prevent recurrent bleeding^[25]. The most common adverse reaction to carvedilol was arterial hypotension, and in rare cases, due to the delay of sodium and water, ascites and edema occurred^[26]. Thus, it is believed that in the absence of contraindications carvedilol may be used for the primary prevention of bleeding from esophageal varices in cirrhotic patients with portal hypertension tolerant to the action of propranolol. Further studies are needed before it enters routine clinical practice.

Antibiotic prophylaxis

Endotoxemia due to the translocation of gram-negative bacteria from the intestine plays an important role in the pathogenesis of complications of portal hypertension under liver cirrhosis, in particular, bleeding from esophageal varices^[27]. To prevent early recurrences of such bleeding, all modern guidelines and consensus decisions point to the need for including antibiotic therapy in treatment. It is recommended to introduce norfloxacin orally, 400 mg every 12 h for 7 d, or, in patients with decompensated liver cirrhosis, introduce ceftriaxone intravenously, 1-2 g/d for 7 d^[28]. In a recent systematic review and meta-analysis, Chavez-Tapia *et al*^[29] showed that the use of antibiotics can significantly reduce overall mortality, the frequency of recurrent bleeding and the duration of hospitalization.

DRUGS POSITIVELY AFFECTING PORTAL HYPERTENSION, WHOSE CLINICAL EFFECTIVENESS IS NOT FULLY PROVEN

Antifibrotic therapy

The object of current research is the search for drugs that affect the basic mechanisms of development of portal hypertension under liver cirrhosis, and, above all, that are able to suppress hepatic fibrogenesis at its early stages. This universal pathophysiological process is a response to damage of various etiologies, resulting in necrosis and apoptosis of hepatocytes, oxidative stress, induction of the inflammatory response by chemokines and cytokines, and recruitment of immune cells. Activated HSC proliferate and migrate into diseased areas of the parenchyma, producing there

excessive amounts of extracellular matrix components. Increased production of matrix metalloproteinases in this pathological situation is blocked by the hypersecretion of their tissue inhibitors. Leading regulators of fibrogenesis are TGF- β_1 , platelet-derived growth factor (PDGF), connective tissue and fibroblast growth factors^[30].

Diffuse fibrosis, the formation of nodules of regenerating hepatocytes, as well as the capillarization of sinusoids impair the delivery of oxygen to the cells of the liver. Hypoxia, developed as a result of the stimulation of hypoxia-inducible factor (HIF) 1 α , contributes to the production of angiogenic factors [placental growth factor (PIGF), vascular endothelial growth factor (VEGF), NO, *etc.*] by activated HSC. This leads to the formation of new blood vessels that bypass sinusoids, leading to the progression of the disease^[31].

Etiological treatment

There are some publications about the positive impact on portal hypertension under liver cirrhosis of antiviral drugs with antifibrotic properties. Pozzi *et al*^[32] described a patient suffering from HBV-related liver cirrhosis (Child-Pugh A), whose HVPG was reduced by 17% as a result of three-month treatment with entecavir.

Correction of the increased hepatic vascular tone

Colmenero *et al*^[33] reported that prolonged treatment of patients with chronic hepatitis C with losartan, a type I specific antagonist of angiotensin II (AT II) receptors (50 mg/d for 18 mo) reduces the activity of NADPH-oxidase, the enzyme that generates oxidative stress. It also reduces gene expression of the main glycoprotein of the extracellular matrix of collagen I, with a positive effect on fibrogenesis. In a systematic review and meta-analysis, Tandon *et al*^[34] noted that reducing hepatic vascular resistance with the antagonists of the renin-angiotensin-aldosterone system (type I blockers of AT II receptors or inhibitors of the angiotensin-converting enzyme) in patients with compensated liver cirrhosis (Child-Pugh A), leads to a slightly smaller reduction of the HVPG than in the case of treatment with non-selective β -adrenergic blocker (17% and 21%, respectively), without significant side effects. However, in decompensated patients, the activation of the systemic renin-angiotensin-aldosterone system caused arterial hypotension, which aggravated hemodynamic impairment and led to the development of renal failure. Similar results were obtained in a randomized controlled clinical trial involving thirty patients with Child-Pugh B liver cirrhosis with large varices. Losartan, like propranolol, improved portal hypertension, but also adversely affected arterial blood pressure with no statistical difference between the two groups^[35].

One of the main causes of endothelial dysfunction

in liver sinusoidal endothelial cells under liver cirrhosis is the deterioration of the bioavailability of the key relaxing factor NO in the hepatic microcirculation. The mechanisms of this phenomenon are diverse. Asymmetrical dimethylarginine, inhibiting the activity of endothelial NO synthase (eNOS), generates peroxynitrite, while reduced expression of tetrahydrobiopterin leads to eNOS producing oxygen instead of NO. The cyclooxygenase (COX) involved in the synthesis of thromboxane A₂ (TXA₂) as well as excessive stimulation of Rho-kinase, inhibit Akt phosphorylation in endothelial cells and significantly inhibit Akt-eNOS signaling. Also, impaired bioavailability of NO may be caused by the weakening of the activity of the superoxide dismutase and increased serum levels of homocysteine due to reduced expression of the enzymes cystathionine- γ -lyase and cystathionine- β -synthase^[36].

Statins, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, in addition to the hypolipidemic properties can improve the endothelial dysfunction of sinusoids^[37]. This is due to the blockade of RhoA/Rho-kinase and the activation of the Akt-eNOS signaling, which increases the bioavailability of NO in cirrhotic livers, leads to a decrease in hepatic vascular resistance and reduction of portal pressure without an adverse effect on systemic hemodynamics^[38]. In addition, it is possible that the positive effect of statins on portal hypertension is at least partially caused by decreased portal-systemic collateral vascular resistance through NO-mediated vascular hyporesponsiveness to ET-1^[39].

In the prospective, randomized, multicenter trial by Abraldes *et al*^[40], simvastatin treatment (20-40 mg/d for 1 mo) of cirrhotic patients resulted in an effective reduction of portal pressure, was safe, and improved perfusion and liver function. This suggests the possibility of clinical use of statins for the treatment of portal hypertension in patients with liver cirrhosis, especially in combination with non-selective β -blockers.

Experiments on rats with a model of biliary cirrhosis showed that inhibitors of phosphodiesterase-5, as a result of increased expression of tetrahydrobiopterin, activity of GTP COX-1, protein levels of phospho-Akt, phospho-eNOS and soluble guanylate cyclase, improved the bioavailability of NO in the liver, eliminated endothelial dysfunction, increased sinusoidal flow and reduced hepatic vascular resistance^[41]. However, in clinical practice, drugs of this type (sildenafil, tadalafil, vardenafil) did not have a positive impact on portal hypertension in most cirrhotic patients, and the resulting deterioration of systemic hemodynamics contributed to kidney dysfunction^[42].

Fiorucci *et al*^[43] comprehensively studied the effect of NCX-1000 (or "Urso-NO"), the liver-specific NO donor, on microcirculation in the cirrhotic liver. In an *in vitro* study, the drug increased cGMP synthesis and the level of nitrite/nitrate in the homogenates

of the liver, as well as the number of total bile acids and tauroursodeoxycholic acid in the bile. In the model of an isolated portal perfused rat liver it raised the sensitivity to α -adrenergic stimuli, and *in vivo* it reduced portal pressure. The authors suggested that, once in the liver, NCX-1000 is included in the metabolism and stimulates the production of biologically active NO. However, despite the good results of experimental studies, clinical trials of the drug in cirrhotic patients showed only systemic hemodynamic effect without affecting portal hypertension^[44].

The selective inhibitor of Rho kinase fasudil can reduce hepatic vascular resistance and HVP in cirrhotic patients with portal hypertension. However, its effect was accompanied by an expressed arterial hypotension^[45].

Theoretically, it is possible to improve the endothelial dysfunction in liver sinusoidal endothelial cells under liver cirrhosis by eliminating the influence of the potent vasoconstrictor ET-1. However, while the nonselective antagonist of endothelial receptors of types ET_A and ET_B bosentan effectively reduced portal pressure in experiments on rats with a liver cirrhosis model^[46], its analogue tezosentan (infusion of 3 mg/h during 2-3 h) did not have a considerable effect on clinically significant portal hypertension in patients with liver cirrhosis in a randomized, double-blind, placebo-controlled multicenter study^[47].

Correction of hyperdynamic circulation and inhibiting the formation of portosystemic collaterals

Disturbance of organ and systemic hemodynamics and the formation process of portosystemic collaterals under portal hypertension begin with splanchnic vasodilation and neovascularization due to the hypoxia of the small intestine mucosa. In this connection, the goal of comprehensive treatment may be to affect the proinflammatory cytokines, chemokines and angiogenic factors (VEGF, PIGF, PDGF and others) that contribute to the development of these disorders^[48].

The orally active multikinase inhibitor sorafenib, used in clinical practice for the treatment of hepatocellular carcinoma, was studied in experiments on rats with models of intra- and extrahepatic portal hypertension. Sorafenib administered orally once a day for 2 wk effectively inhibited VEGF, PDGF, and Raf signaling pathways, and produced several protective effects by inducing an approximately 80% decrease in splanchnic neovascularization and a marked attenuation of hyperdynamic splanchnic and systemic circulations, as well as an 18% decrease in the extent of portosystemic collaterals. In cirrhotic rats, sorafenib treatment also resulted in a 25% reduction in portal pressure, as well as a remarkable improvement in liver damage and intrahepatic fibrosis, inflammation, and angiogenesis. Notably, beneficial effects of sorafenib against tissue damage and inflammation

were also observed in splanchnic organs^[49]. It was also found that the positive effect of sorafenib on portal hypertension was more significant when combined with propranolol^[50].

Pinter *et al*^[51] assessed the effect of sorafenib on portal hypertension in 13 patients with liver cirrhosis and hepatocellular carcinoma (Child-Pugh A and B). The drug was administered in a daily dose of 800 mg twice a day for two weeks. A reduction of the HVPG by over 20% from the baseline was achieved in four patients, with no serious dysfunction of the liver. Despite the positive results, studies on the safety and efficacy of lower doses of the drug in cirrhotic patients with portal hypertension without hepatocellular carcinoma, are not yet available.

The ability to influence extrahepatic mechanisms of portal hypertension pathogenesis was found in some natural compounds with antioxidant activity. It turned out that ascorbic acid and dark chocolate can reduce the postprandial increase in portal pressure, and the green tea made from the leaves of *Camellia sinensis*, decreases the severity of portosystemic collaterals and mesenteric angiogenesis in rats with a liver cirrhosis model^[52-54].

Correction of endotoxemia

Portal hypertension is most severe in cirrhotic patients with concomitant manifestations of the systemic inflammatory response syndrome. The associated endotoxemia due to the translocation of gram-negative bacteria from the intestine occurs in approximately 30%-40% of decompensated patients, who are classified in this clinical situation as "critically ill cirrhotics". The endotoxemia is the cause of many complications of portal hypertension; it increases the mortality by a factor of four, which is often due to the spontaneous bacterial peritonitis and hepatorenal syndrome^[55]. Stimulating innate immune signals with pathogen-associated molecular patterns (PAMPs), leads to the activation on the cell surface of Toll-like receptors (TLR) that are widely present in the liver. The first to react to the exposure to PAMPs are Kupfer cells, which because of TLR-signaling acquire a proinflammatory phenotype and produce excessive amounts of cytokines, which exacerbates portal hypertension under liver cirrhosis^[56]. On the contrary, the high-density lipoprotein administration attenuates liver proinflammatory response, restores liver eNOS activity, and lowers portal pressure in rats with a liver cirrhosis model^[57].

Once in the portal circulation, endotoxin enters the systemic circulation through the network of portosystemic collaterals or by-passing the Kupfer cells. Therefore, bacterial translocation in patients with liver cirrhosis leads not only to infectious complications, but also to blood circulation disorders typical for portal hypertension. These are caused by the endotoxin stimulating NO production in the arterial bed, contributing to splanchnic and systemic vasodilation,

exacerbating hyperdynamic circulation and increasing portal pressure^[58]. In particular, a direct correlation was observed between the level of endotoxemia in cirrhotic patients, the degree of esophageal varices and whether there is bleeding from them^[59].

In connection with that, there is some discussion about the practicality of treating portal hypertension with medications normalizing the intestinal flora and preventing its translocation. Indeed, in patients with alcohol-related liver cirrhosis, oral administration of norfloxacin (800 mg/d for 4 wk) reduced the level of serum endotoxin, which contributed to the reduction of portal pressure and improved the hyperdynamic circulation^[60]. In addition, its long-term administration (400 mg/d for one year) to decompensated patients prevented the development of hepatorenal syndrome and significantly improved survival rate^[61].

Reduced severity of endotoxemia and an 18% decrease in the HVPG was observed in a prospective study including patients with alcohol-related decompensated liver cirrhosis. The decontamination of the intestine in these patients was done with the nonabsorbable antibiotic rifaximin (1200 mg/d for 28 d)^[62]. In addition, long-term rifaximin administration in these patients is associated with reduced risk of developing complications of portal hypertension and improved survival^[63]. Apart from affecting the intestinal microflora, the positive effect of rifaximin on portal hypertension can be explained by the inhibition of the binding of lipopolysaccharide with TLR4 on the surface of the HSC, which contributes to their inactivation, the breaking of the fibronectin-mediated interaction with the SEC and eventually the suppression of fibrogenesis and angiogenesis in the liver^[64].

The therapeutic effect of probiotics under portal hypertension is ambiguous. In particular, the combined probiotic VSL#3, which contains eight different strains (*Bif. breve*, *Bif. longum*, *Bif. infantis*, *L. acidophilus*, *L. plantarum*, *L. casei*, *L. bulgaricus*, *Streptococcus thermophilus*) can stabilize the intestinal epithelial barrier, reduce the bacterial translocation and systemic endotoxemia. This reduces the production of proinflammatory cytokines and NO, eliminates endothelial dysfunction of mesenteric arteries caused by vascular oxidative stress and inactivates the local renin-angiotensin system^[65].

In a pilot study involving 8 patients with compensated liver cirrhosis (Child-Pugh A)^[66] and in a randomized, double-blind, placebo-controlled study, including 7 patients with decompensated liver cirrhosis (Child-Pugh B and C)^[67], monotherapy with the probiotic VSL#3 at a dose of 3600 billion CFU/d for 2 mo had no significant impact on clinically important portal hypertension.

In a randomized double-blind placebo-controlled trial in parallel groups, including 94 cirrhotic patients having large esophageal varices without history of variceal bleeding, changes in the HVPG were studied after administering propranolol, singly or in

Table 1 Drugs that can affect the portal hypertension, the effect of which was studied in the experiment

Ref.	Drugs	Experimental model	Effects
Zhao <i>et al</i> ^[69]	Diammonium glycyrrhizinate	CCl ₄ /IPPRLs	Improves the bioavailability of NO in portal triads
Di Pascoli <i>et al</i> ^[70]	Resveratrol	CCl ₄	Improves vasodilatory response to acetylcholine, decreases TXA ₂ production, increases endothelial NO and reduces hepatic fibrosis
Yang <i>et al</i> ^[71]	Ursodeoxycholic acid	BDL	Suppresses hepatic TXA ₂ production and lipid peroxidation. An increase in antioxidative defence leading to the prevention of hepatic fibrosis
Rodríguez-Vilarrupla <i>et al</i> ^[72]	Fenofibrate	CCl ₄	Reduces hepatic fibrosis, improves vasodilatory response to acetylcholine, reduces COX-1 expression and TXB ₂ production, increases NO bioavailability in SEC
Hsieh <i>et al</i> ^[73]	Aliskiren	BDL	Ameliorates the angiotensin II induced intrahepatic vasoconstriction
Luo <i>et al</i> ^[74]	Spironolactone	BDL	Inhibits hepatic fibrosis, ROCK-2 activity and activates NO/PKG pathway
Gao <i>et al</i> ^[75]	Celecoxib	TAA	Inhibits hepatic fibrosis and angiogenesis. The anti-angiogenesis effect associates with the modulation of VEGF/VEGFR-2
Rosado <i>et al</i> ^[76]	Terutroban	CCl ₄ /BDL	In CCl ₄ -cirrhotic rats decreases hepatic fibrosis, in BDL-rats enhances eNOS-dependent vasodilatation
Wang <i>et al</i> ^[77]	Rapamycin	BDL	Ameliorates intrahepatic inflammation and fibrosis, improves liver function
Laleman <i>et al</i> ^[78]	Nitroflurbiprofen/Flurbiprofen	TAA/IPPRLs	Decreases hepatic TXA ₂ production and increases intrahepatic nitrate/nitrite level
Yang <i>et al</i> ^[79]	Vitamin E	BDL	Asymmetric dimethylarginine improves hepatic endothelial dysfunction by a vitamin E through an increase of NO bioavailability
Liu <i>et al</i> ^[80]	Blebbistatin	<i>In vitro</i>	Inhibits the contraction and accelerates migration of HSC
Verbeke <i>et al</i> ^[81]	Obeticholic acid	BDL	Decreases hepatic vascular resistance by increasing eNOS activity
Steib <i>et al</i> ^[82]	Montelukast	TAA/BDL	Inhibiting the cysteinyl leukotrienes receptors reduces hepatic vascular resistance
Xu <i>et al</i> ^[83]	Salvianolic acid B	DMN/ <i>In vitro</i>	Reduces HSCs contractility
Fernandez <i>et al</i> ^[84]	Rapamycin+Gleevec	PPVL	Reduces splanchnic neovascularization
Schwabl <i>et al</i> ^[85]	Pioglitazone	BDL/PPVL	Decreases portosystemic shunting
Fallowfield <i>et al</i> ^[86]	Relaxin	CCl ₄ /BDL/ <i>In vitro</i>	Down-regulates HSC- myofibroblast contractile filament expression and contractile function
Lin <i>et al</i> ^[87]	Bivanib alaninate	BDL/ IPPRLs/ <i>In vitro</i>	Suppresses and ameliorates fibrogenic and angiogenic markers in the serum and liver. Inhibits the TGFβ ₁ -induced HSCs contraction/migration and VEGF-induced SECs angiogenesis

IPPRLs: Isolated portal perfused rat livers; BDL: Bile-duct ligated rats; TAA: Thiocetamide-induced cirrhosis in rats; DMN: Dimethylnitrosamine-induced cirrhosis in rats; PPVL: Partial portal vein ligation in rats.

combination with either VSL#3 (900 billion CFU/d) or norfloxacin (400 mg/d). The treatment was carried out for 2 mo. The initial propranolol dose of 40 mg/d was increased by 20-40 mg every two days (to the maximum of 320 mg/d) until the heart rate of 55 BPM or the occurrence of side effects. It turned out that the combination of propranolol with the probiotic or the antibiotic was more effective in reducing portal pressure than the exclusive use of a nonselective β-adrenergic blocker (by 19%, 18% and 11%, respectively), was safe and well tolerated by patients^[68].

Apart from the mentioned drugs, there are some others whose action on portal hypertension was studied only in experiments (Table 1) and clinical trials are necessary for their final assessment.

In conclusion, it should be noted that dissatisfaction with the current methods of pharmacotherapy of portal hypertension and advances in the study of its pathogenesis under liver cirrhosis have contributed to the search for effective drugs aimed at the prevention and treatment of the complications characteristic of

this syndrome. It can be expected that the practical implementation of the new methods will lead to some progress in solving this problem.

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