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ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Somchai Amornyotin, MD, Associate Professor, Staff Physician, Department of Anesthesiology and Siriraj Gastrointestinal Endoscopy Center, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

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Ze-Mao Gong, Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
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MINIREVIEWS

Antiangiogenic therapy for portal hypertension in liver cirrhosis: Current progress and perspectives

Dmitry Victorovich Garbuzenko, Nikolay Olegovich Arefyev, Evgeniy Leonidovich Kazachkov

Dmitry Victorovich Garbuzenko, Department of Faculty Surgery, South Ural State Medical University, Chelyabinsk 454092, Russia

Nikolay Olegovich Arefyev, Evgeniy Leonidovich Kazachkov, Department of Pathological Anatomy and Forensic Medicine, South Ural State Medical University, Chelyabinsk 454092, Russia

ORCID number: Dmitry Victorovich Garbuzenko (0000-0001-9809-8015); Nikolay Olegovich Arefyev (0000-0002-1770-064X); Evgeniy Leonidovich Kazachkov (0000-0002-2008-7671).

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Correspondence to: Dmitry Victorovich Garbuzenko, MD, PhD, Professor, Department of Faculty Surgery, South Ural State Medical University, PO Box 12317, Chelyabinsk 454080, Russia. garb@inbox.ru
Telephone: +7-909-7459826
Fax: +7-351-2687772

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Abstract

Developing medicines for hemodynamic disorders that are characteristic of cirrhosis of the liver is a relevant problem in modern hepatology. The increase in hepatic vascular resistance to portal blood flow and subsequent hyperdynamic circulation underlie portal hypertension (PH) and promote its progression, despite the formation of portosystemic collaterals. Angiogenesis and vascular bed restructurization play an important role in PH pathogenesis as well. In this regard, strategic directions in the therapy for PH in cirrhosis include selectively decreasing hepatic vascular resistance while preserving or increasing portal blood flow, and correcting hyperdynamic circulation and pathological angiogenesis. The aim of this review is to describe the mechanisms of angiogenesis in PH and the methods of antiangiogenic therapy. The PubMed database, the Google Scholar retrieval system, and the reference lists from related articles were used to search for relevant publications. Articles corresponding to the aim of the review were selected for 2000-2017 using the keywords: "liver cirrhosis", "portal hypertension", "pathogenesis", "angiogenesis", and "antiangiogenic therapy". Antiangiogenic therapy for PH was the inclusion criterion. In this review, we have described angiogenesis inhibitors and their mechanism of action in relation to PH. Although most of them were studied

only in animal experiments, this selective therapy for abnormally growing newly formed vessels is pathogenetically reasonable to treat PH and associated complications.

Key words: Liver cirrhosis; Portal hypertension; Pathogenesis; Angiogenesis; Antiangiogenic therapy

Core tip: This review describes the role of angiogenesis in the pathogenesis of portal hypertension in liver cirrhosis and the prospects of antiangiogenic therapy. The analysis of the data showed that angiogenesis plays an important role in the pathogenesis of cirrhosis and accompanies portal hypertension, underlying its development and causing related complications. Although most of angiogenesis inhibitors were studied only in animal experiments, this selective therapy for abnormally growing newly formed vessels is pathogenetically reasonable to treat portal hypertension and associated complications.

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INTRODUCTION

Developing medicines to treat hemodynamic disorders that are characteristic of liver cirrhosis and promote portal hypertension (PH) and related complications is a relevant problem in modern hepatology. In accordance with the current clinical recommendations, nonselective β-adrenoblockers are the drugs of choice[1]. However, their influence on portal pressure is variable. A number of studies showed that they did not lead to a clinically significant decrease in portal pressure, and the weakening of their therapeutic effect was noted in 50%-70% of cases in the long-term period. Also, the question of the appropriateness of using nonselective β-adrenergic blockers in patients with decompensated cirrhosis has not been finally resolved[2].

Ideally, the pharmacotherapy of PH should lessen the severity of morphofunctional disorders in the liver, contributing to the reduction of the vascular resistance to portal blood flow. Also, it should successfully correct a hyperdynamic circulatory state. As a result, the hepatic venous pressure gradient (HVPG), the most accurate equivalent of portal pressure, should be reduced to less than 12 mmHg or be 20% lower than an original value. In addition, it is necessary to avoid arterial hypotension and at the same time reduce the influx of splanchnic blood into the portal vein, keeping unchanged the portal blood flow, which participates in liver perfusion[3].

Angiogenesis plays an important role in the pathogenesis of many chronic liver diseases, including fibrosis, cirrhosis, and hepatocellular carcinoma[4]. It can also accompany PH, underlying its development and causing related complications. Indeed, the newly formed blood vessels, which bypass sinusoids in response to the gross morphofunctional rearrangement of the liver in cirrhosis, fail to provide oxygen and nutrients to the tissues, which worsens the course of the disease and increases hepatic vascular resistance to portal blood flow[5]. Further progression of PH is a consequence of complex processes including angiogenesis, vascular remodeling, and endothelial dysfunction, which contribute to splanchnic congestion, portosystemic shunt formation, and a hyperdynamic circulatory state[6] (Figure 1). From this, it can be inferred that antiangiogenic therapy, which is selectively aimed at suppressing newly formed vessels' formation and growth, is a pathogenetically grounded method of treating PH and associated complications[7].

The efforts to develop angiogenesis inhibitors began in the 1970s at Harvard University under the guidance of Judah Folkman. The drugs were actively introduced into clinical practice a decade after the first were developed[8].

INHIBITORS OF INTRAHEPATIC ANGIOGENESIS

One of the two main mechanisms in the formation of new blood vessels in the liver in cirrhosis is associated with an increased expression of pro-angiogenic growth factors, cytokines, and matrix metalloproteinases in the presence of chronic inflammation. Proinflammatory mediators produced by Kupffer cells, mast cells, and leukocytes may manifest an angiogenic response at the expense of hypoxia-inducible factor-1α (HIF-1α) induction and increased transcription activity[9]. HIF-1α activates hepatic stellate cells (HSC), which leads to the development of various angiogenic and fibrogenic factors, promoting both angiogenesis and liver fibrosis[10]. At the same time, diffuse fibrosis, the formation of regenerative nodules, and also the capillarization of sinusoids cause an increase in hepatic vascular resistance and impair oxygen delivery to liver cells[11]. Accumulation of HIFs, in particular HIF-1α, increases the expression of vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang1), and their related receptors on activated HSC. This leads to recruitment and stimulation of sinusoidal endothelial cells (SEC), which stabilizes the newly formed vessels and ensures their strength. In turn, SEC produce platelet-derived growth factor (PDGF) and transforming growth factor-β1 (TGF-β1), contributing to the recruitment and migration of HSC, a process that involves reactive oxygen species-dependent activation of the extracellular

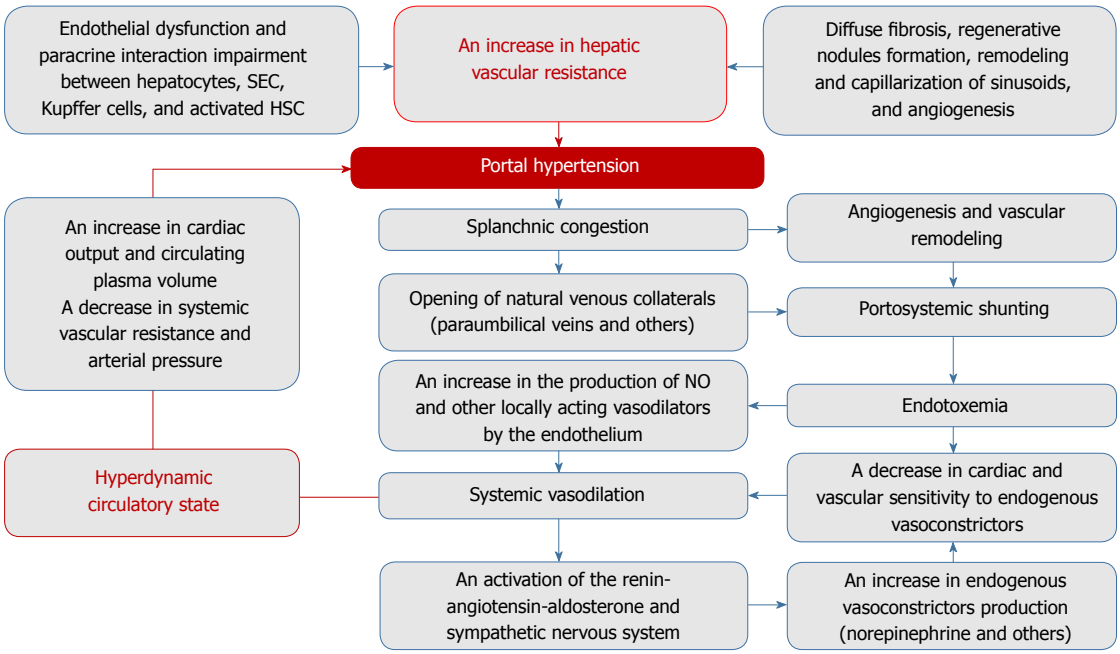

Figure 1 Potential mechanisms of portal hypertension pathogenesis in cirrhosis. The newly formed blood vessels, which bypass sinusoids in response to the gross morphofunctional rearrangement of the liver in cirrhosis, fail to provide oxygen and nutrients to the tissues. With endothelial dysfunction and impaired paracrine interaction between hepatocytes, sinusoidal endothelial cells (SEC), Kupffer cells, and activated hepatic stellate cells (HSC), this increases hepatic vascular resistance to portal blood flow. Further progression of portal hypertension is a consequence of complex processes including angiogenesis, vascular remodeling, and endothelial dysfunction, which contribute to splanchnic congestion, systemic vasodilation, and portosystemic shunt formation. The subsequent hyperdynamic circulatory state worsens the course of the disease.

signal-regulated kinase (ERK) pathway and c-Jun NH2-terminal kinases (JNK) followed by HIF-1α-dependent synthesis of VEGF[12].

Tyrosine kinase inhibitors

The introduction of antiangiogenic therapy into hepatological practice began with the treatment of hepatocellular carcinoma, a well-vascularized tumor that needs intense angiogenic activity for its development[13]. The most studied drug used for this purpose is sorafenib, a multi-targeted inhibitor of receptor and non-receptor tyrosine kinases, which are responsible for transmitting various signals to cells, including proliferative stimuli. The antitumor and antiangiogenic effect of sorafenib is achieved mainly through the suppression of the Raf/MEK/ERK signaling pathway and blockade of signaling from the receptors of VEGF (VEGFR), PDGF (PDGFR), and c-kit (SCFR)[14].

Experimental studies have shown the antiangiogenic effect of sorafenib during the early stage of hepatic fibrosis[15]. In animals with various models of cirrhosis, it had positive effects on some pathogenetic pathways of fibrogenesis and angiogenesis in the liver by blocking the receptor tyrosine kinases located on the surface of HSC, the expression of which, especially VEGFR and PDGFR, was increased[16] (Figure 2): (1) The suppression of activated HSC proliferation and the activation of apoptosis; (2) 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 ratio of Bcl-2 to Bax; (3) an increase in the ratio of matrix metalloproteinases to the tissue inhibitor of matrix metalloproteinases, and also a decrease in the synthesis of collagen by HSC; (4) the inhibition of phosphorylation of ERK, Akt, and ribosomal protein kinase S6 with a molecular mass of 70 kDa (p70S6K)[17]; and (5) the disturbance of the Kruppel-like factor 6–Ang1–fibronectin molecular triad functioning[18]. Sorafenib decreased the severity of inflammation, fibrogenesis, and angiogenesis in rats with biliary cirrhosis, which led to a reduction in hepatic vascular resistance to portal blood flow[19].

Another multi-targeted tyrosine kinase inhibitor sunitinib is less studied but known to block VEGFR1/2/3, PDGFR-α/β, fibroblast growth factor receptor (FGFR), and c-kit signaling[20]. In addition, an *in vitro* study by Majumder *et al*[21] showed that sunitinib can slow HSC collagen synthesis by 47%, reduce HSC contractility by 65%, and decrease cellular migration by 28%, as well as inhibit the angiogenic capacity of SEC.

Branivib is a double inhibitor of VEGFR and FGFR signaling. It significantly suppressed intrahepatic angiogenesis and reduced PH in rats with biliary cirrhosis[22]. Additionally, it improved blood circulation in the liver and hindered the formation of ascites in rats with liver cirrhosis caused by nonalcoholic steatohepatitis[23].

Statins

The positive effect of statins on hepatic fibro- and angiogenesis in cirrhosis is associated with the induction

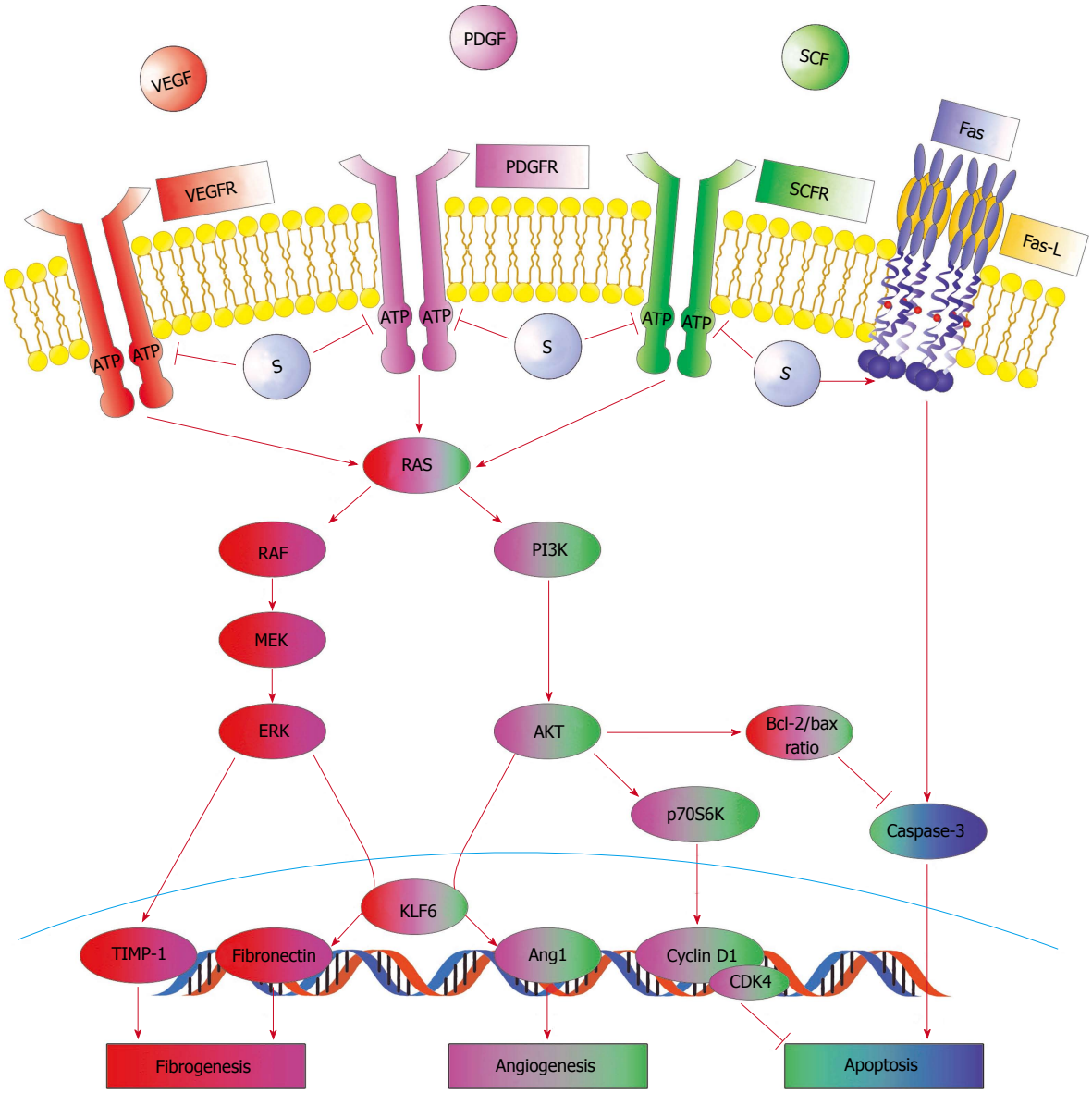

Figure 2 Positive effects of sorafenib on some pathogenetic pathways of fibrogenesis and angiogenesis in the liver. Sorafenib (S) blocks the ATP-binding site of the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and stem cell growth factor receptor (SCFR) tyrosine kinases located on the surface of hepatic stellate cells (HSC), inhibiting the two main cellular pathways of the RAS protein. At the same time, sorafenib increases the expression of Fas and its ligand. This decreases the severity of fibrogenesis and angiogenesis and increases apoptosis, leading to a reduction in hepatic vascular resistance to portal blood flow.

of KLF2 in SEC[24]. KLF2 is a member of a family of widely expressed transcription factors that regulate cell and tissue growth. KLF2 is well represented in the vascular endothelium and is necessary for the normal development of vessels; in addition, it is a well-known antiangiogenic factor that modulates the severity of many endothelial vasoprotective genes[25]. KLF2 can effectively inhibit HIF-1α, reducing the expression of such proangiogenic factors as VEGF and Ang2[26].

The mechanical stimuli generated by shear stress are the main physiological impulse for triggering and maintaining endothelial KLF2 expression[27]. In the cirrhotic liver, KLF2 expression was elevated in both SEC[28] and activated HSC[29]. This serves as a compensatory mechanism aimed at eliminating vascular dysfunction and preventing angiogenesis by suppressing the proliferation and migration of SEC, as well as downregulating the ERK1/2 signaling pathway to inhibit the formation of tubular structures[30].

In an *in-vitro* study conducted by Miao *et al*[31], simvastatin eliminated the pro-angiogenic environment for TGF-β-activated HSC as a result of the following processes: (1) The reduction of cell migration and proliferation; (2) the inhibition of the α-smooth muscle actin expression, and the elevation of mRNA and KLF2 levels in HSC; (3) an increase in the production of endothelial nitric oxide synthase (eNOS) and suppression of the various proangiogenic proteins expression in HSC, such as VEGF, HIF-1α, and pro-inflammatory nuclear factor kappa B (NF-κB); and (4) the reduction

of the hyperactivity of interferon γ, which participates in angiogenesis. In rats with CCL_4-induced liver cirrhosis, it was noted that statins (atorvastatin, mevastatin, simvastatin, and lovastatin) enhanced the effect of KLF2. By doing this, they deactivated SEC and reduced the severity of fibrosis and associated angiogenesis, thereby exerting a positive effect on PH[32].

Rifaximin

Endotoxemia, which is due to the translocation of gram-negative bacteria from the intestine, plays an important role in the pathogenesis of both cirrhosis and associated complications[33]. During the development of cirrhosis, bacterial lipopolysaccharide influences Kupffer cells and HSC. Nevertheless, SEC is affected first. Toll-like receptors 4 (TLR4), which are located on their surface and capable of binding bacterial lipopolysaccharide, is involved in fibrosis-associated angiogenesis. These receptors manifest such properties through the related cytosolic adapter protein MyD88, which is involved in the production of extracellular protease regulating the invasive ability of SEC[34].

In mice with biliary cirrhosis, it was shown that rifaximin, a nonabsorbable antibiotic with broad antimicrobial activity against aerobic and anaerobic gram-negative bacteria, reduced the severity of fibrosis and angiogenesis in the liver by inhibiting bacterial lipopolysaccharide binding to TLR4. As a consequence, it reduced PH[35]. This drug is already used to treat hepatic encephalopathy. It has an acceptable safety profile when applied in patients with chronic liver diseases and is approved by the US Food and Drug Administration[36]. The experimental study[35] may be a basis for evaluation of rifaximin in other complications of cirrhosis.

Largazole

The histone deacetylase inhibitor largazole is a natural compound derived from marine cyanobacteria Symploca sp. With a strong antiproliferative and cytotoxic effect, it has a wide spectrum but differential activity against several different lines of cancer cells[37]. In addition, in experimental studies *in vitro* and *in vivo*, largazole attenuated the severity of liver fibrosis and associated angiogenesis through numerous independent mechanisms: (1) The reduction of VEGF production by HSC; (2) the inhibition of VEGF-stimulated HSC proliferation; (3) the downregulation of TGF-β1- and VEGF-induced Akt phosphorylation in activated HSC, as well as the downregulation of VEGFR2-dependent p38MAPK phosphorylation in SEC; and (4) the suppression of CD34, VEGF, and VEGFR2 expression[38]. The ability of largazole to affect the main fibrogenic and angiogenic pathways in the cirrhotic liver can be used to test its effectiveness in PH.

Ribavirin

In addition to antiviral activity against certain DNA- and RNA-containing viruses, ribavirin may have a positive effect on the morphological changes underlying the development of cirrhosis[39]. In addition, at therapeutic concentrations, it is able to inhibit angiogenesis both *in vitro* and *in vivo*, which is due to the inhibition of inosine-5'-monophosphate dehydrogenase 1 activity and a decrease in tetrahydrobiopterin, NO, and cGMP levels in SEC[40].

INHIBITORS OF EXTRAHEPATIC ANGIOGENESIS

Disturbances of organ and systemic hemodynamics and the development of portosystemic collateral circulation in PH begin with splanchnic vasodilation and neovascularization caused by hypoxia of intestinal mucosa and pro-inflammatory cytokines, chemokines, and angiogenic factors, such as VEGF, PDGF, the placental growth factor (PlGF), and others[41]. It was traditionally thought that portosystemic shunts are formed when increased portal pressure "opens" pre-existing vessels in the areas of embryonic connection between the portal and systemic circulation. This paradigm was challenged by Fernandez, who first reported that portosystemic collaterals in PH are formed due to active angiogenesis. It was shown in an animal model of prehepatic PH induced by partial portal vein ligation that the blockade of VEGFR-2 with anti-VEGFR-2 monoclonal antibody for 5-7 d and inhibition of VEGF/VEGFR-2 signalization using autophosphorylation inhibitor VEGFR-2 for 5 d after the operation resulted in 50% reduction of portosystemic collateral vessel formation[42,43]. Blockade of NAD(P)H also contributed to this owing to the reduced splanchnic expression of VEGF, VEGFR-2, and CD31[44].

It should be noted that VEGF is of the greatest importance only at the initial stages of angiogenesis, when it activates endothelial cell proliferation and the subsequent formation of endothelial tubules. Vascular maturation is modulated mainly by PDGF, which regulates the introduction of endothelial tubules into the population of intramural cells and pericytes, thus stabilizing the newly formed vasculature[45]. The simultaneous suppression of the signaling caused by both VEGF and PDGF appears more promising than suppressing them individually.

Tyrosine kinase inhibitors

Fernandez *et al*[46] studied the combined effect of rapamycin (mTOR inhibitor) and glivec (tyrosine protein kinase inhibitor) on VEGF and PDGF signaling, respectively, in rats with extrahepatic PH caused by partial portal vein ligation and with well-developed portosystemic collateral circulation. It was noted that rapamycin and glivec in combination markedly reduced the splanchnic neovascularization and pericyte coverage of new vessels through the decreased expression of VEGF, VEGFR2, CD31, PDGF, PDGFR-β, and α-smooth muscle actin. In addition, there was a reduction of

portal pressure and blood flow along the superior mesenteric artery by 40% and 30% from the baseline level, respectively.

Similar results were obtained by Mejias *et al*[19], who found that multi-kinase inhibitor sorafenib triggered blockade of VEGF and PDGF signaling transduction and the Raf/MEK/ERK signaling pathways. Sorafenib significantly reduced intraorgan and systemic blood flow, and increased splanchnic neovascularization by 80% and portosystemic shunting by 18%. This led to a reduction in hepatic vascular resistance and decrease in portal pressure by 25% from the baseline. It was also noted that the positive effect of sorafenib on PH was more significant when it was combined with propranolol[47].

Somatostatin and its synthetic analogs

Somatostatin is a cyclic 14-amino acid peptide, which is secreted by nerve, endocrine, and enteroendocrine cells in the hypothalamus and digestive system (in the stomach, intestine, and pancreatic δ-cells). Somatostatin and its synthetic analogs (octreotide, vapreotide, and others) are used in patients with cirrhosis to treat bleeding from esophageal varices by affecting both intra- and extrahepatic mechanisms of PH[48].

The ability of octreotide to inhibit cell proliferation and neovascularization through the high-affinity somatostatin subtype receptor 2 (SSTR2) was an impetus for studying its antiangiogenic properties in various diseases[49]. In studies involving rats with extrahepatic PH caused by partial portal vein ligation, octreotide significantly weakened the expression of VEGF and CD31 in the internal organs, reduced the development of splanchnic neovascularization by 64%, and lessened the severity of a portosystemic collateral circulation by 16%. At the same time, its angioinhibitory effect manifested only in the first four days of the experiment and completely disappeared after a week, as PH progressed. This is possibly due to a decrease in SSTR2 expression in mucosa, intestinal vessels, and portosystemic collaterals[50].

Spironolactone

Pathophysiological disturbances inherent to PH underlie the occurrence of ascites in cirrhosis. Systemic arterial vasodilation and the activation of various neurohormonal pathways, including the renin-angiotensin-aldosterone system, caused renal dysfunction. This decreases Na^+ and water excretion and reduces the glomerular filtration rate. The drug of choice for treatment is spironolactone, an antagonist of aldosterone, a mineralocorticoid, that mediates the reabsorption of Na^+ and water in the distal part of the nephron[51]. In addition to the important role in maintaining water-salt metabolism, aldosterone has angiogenic properties. In particular, it enhances ischemia-induced neovascularization[52], stimulates pathological angiogenesis in the retina[53], and promotes the proliferation of endothelial cells of the heart[54] by activating angiotensin Ⅱ signaling. At the same time, its antagonist spironolactone inhibits these processes both *in vitro* and *in vivo*[55]. In rats with biliary cirrhosis, spironolactone significantly reduced the degree of mesenteric angiogenesis and portosystemic shunting by suppressing the VEGF signal transduction pathway[56].

N-acetylcysteine

Because hypoxia serves as the main inducer of angiogenesis both under physiological and pathological conditions, angiogenesis inhibitors may be drugs with antioxidant properties. One of them is N-acetylcysteine, which is a derivative of amino acid cysteine, the thiol groups of which directly interact with electrophilic groups of free radicals. N-acetylcysteine can also enhance the activity of glutathione-S-transferase, glutathione peroxidase, glutathione reductase, and a number of other enzymes involved in maintaining the oxidant/antioxidant balance[57].

Long-term application of N-acetylcysteine in rats with biliary cirrhosis lessened oxidative stress in the mesentery of the small intestine, reduced the level of circulating inflammatory cytokines, and inhibited mesenteric angiogenesis by decreasing angiogenic marker expression (VEGF, VEGFR2, Ang1, and CD31). This eventually improved splanchnic and systemic hemodynamics.

In addition, N-acetylcysteine inhibited VEGF-induced endothelial tubule formation and endothelial cell migration by suppressing tumor necrosis factor-α (TNF-α) and Akt/eNOS/NO angiogenic signaling cascade *in vitro*. It also reduced the number of reactive oxygen species (including reactive compounds of thiobarbituric acid and malondialdehyde) and inflammatory cytokines in the human umbilical vein endothelial cell supernatant[58].

Endothelin receptor blockers

Endothelin-1 (ET-1) is one of the mediators whose synthesis is enhanced in conditions of tissue hypoxia. It belongs to the endothelin family, which includes two more homologous oligopeptides (ET-2 and ET-3). Endothelins are the products of the proteolysis of their precursor "large endothelin", which is driven by the endothelin-converting enzyme. They act through two types of G-protein-coupled receptors: type A (ET_A) and type B (ET_B). Type B (ET_B) has two isoforms: ET_{B1} and ET_{B2}. ET_A are located primarily on membranes of vascular smooth muscle cells, whereas ET_B are present on both endothelial and smooth muscle cells.

ET-1, the most studied potent vasoconstrictor, is produced by vascular endothelial and smooth muscle cells. It is directly involved in intra- and extrahepatic mechanisms of PH pathogenesis, and its circulating level is increased in cirrhosis because of "large endothelin" hyperproduction and increased expression of endothelin-converting enzyme[59]. Experimental studies have shown that ET-1 induces angiogenic responses in

cultured endothelial cells through endothelial ET_B-type receptors and, in combination with VEGF, stimulates neovascularization *in vivo*[60]. The nonselective endothelin receptor blocker bosentan and the selective ET_A receptor blocker ambrisentan reduced the degree of mesenteric angiogenesis and portosystemic shunting in rats with biliary cirrhosis by suppressing inducible nitric oxide synthase (iNOS), cyclooxygenase 2, VEGF and VEGFR2, and Akt signaling[61].

Pioglitazone

Pioglitazone, a potent selective agonist of peroxisome proliferator-activated receptors-γ (PPAR-γ), is able to reduce the level of systemic inflammation in patients with a high cardiovascular disease risk. It blocks the activity of pro-inflammatory genes by post-transcriptional modification of their products (by attaching small SUMO proteins to them) and suppresses NF-κB expression by transrepression. All PPAR isomers (PPAR-α, PPAR-β/-δ, and PPAR-γ) are anti-inflammatory nuclear transcription factors and NF-κB antagonists. Dominant negative mutation of PPAR-γ leads to systemic inflammation and rapid development of related diseases: arterial hypertension, atherosclerosis, type 2 diabetes, nonalcoholic steatohepatitis, psoriasis, and premature aging[62].

In addition to systemic inflammation reduction, PPAR-γ agonists are also capable of inhibiting oxidative stress and angiogenesis[63]. In rats with models of biliary cirrhosis and extrahepatic PH caused by partial portal vein ligation, pioglitazone reduced the degree of portosystemic shunting by 22%-30% by suppressing angiogenic and pro-inflammatory cytokines, chemokines, and growth factors (VEGF, PDGF, and PIGF)[64].

Thalidomide

Thalidomide, a glutamic acid derivative with anti-angiogenic, anti-inflammatory, and immunomodulatory properties, is able to hinder TNF-α/interleukin-1β production for which activated immune cells are responsible[65]. It was also shown in rats with biliary cirrhosis that thalidomide blocked the TNFα-VEGF-NOS-NO pathway by downregulating elevated inflammasome expression in the intestinal and mesenteric tissues, which weakened mesenteric angiogenesis and portosystemic shunting[66].

Polyphenols

The possibility of influencing the pathogenetic mechanisms of extrahepatic angiogenesis was found in polyphenols, the chemicals of plant origin with a strong antioxidant effect.

The tea catechins extracted from the dried leaves of *Camellia sinensis* reduced the severity of mesenteric angiogenesis and portosystemic shunting in rats with biliary cirrhosis by reducing HIF-1α expression, Akt signaling, and VEGF synthesis[67].

2′-hydroxyflavonoid, which is contained in citruses, prevented the formation of new splanchnic vessels and portosystemic collaterals in rats with thioacetamide-induced liver cirrhosis by downregulating apoptosis[68].

The long-term use of curcumin, a polyphenol extracted from turmeric roots, improved the course of PH in liver cirrhosis by positively affecting liver fibrosis and reducing portal influx. These effects were achieved through inhibiting mesenteric angiogenesis and restoring mesenteric vessel contractility, as well as decreasing the degree of portosystemic collateral circulation and hyperdynamic circulatory state. Moreover, its favorable effects on the splanchnic and systemic blood flow included the suppression of VEGF, cyclooxygenase 2, and eNOS[69].

CLINICAL EXPERIENCE OF ANTIANGIOGENIC THERAPY FOR PH

The effect of the drugs described above was studied only in experiments involving animals (Tables 1 and 2), and only tyrosine kinase inhibitors were tested as an antiangiogenic therapy in patients with cirrhosis and PH.

Coriat *et al*[70] were the first to assess the effect of sorafenib on the portal and systemic hemodynamics, in seven patients with cirrhosis and hepatocellular carcinoma. Five of them had Child–Turcotte–Pugh (CTP) class A, and two had CTP class B. Sorafenib was administered for one month at 400 mg twice a day. In one patient, this was first reduced to 400 mg once a day and then to 400 mg every two days because side effects appeared. A decrease in portal blood flow by at least 36% was noted, while no changes in blood flow were found in the azygos vein and abdominal aorta.

In a pilot study, Pinter *et al*[71] investigated the effects of sorafenib on HVPG and systemic hemodynamics, as well as the expression of mRNA genes involved in fibrogenesis, angiogenesis, and inflammation in the liver in 13 patients suffering from cirrhosis and hepatocellular carcinoma (10 patients had CTP class A and three patients had CTP class B). The drug was administered at 400 mg twice a day for two weeks. Four of the 11 patients with PH (eight of whom had clinically significant PH) had a reduction in HVPG by more than 20% from the baseline values and, in addition, a decrease in the levels of mRNA, VEGF, PDGF, PIGF, RhoA kinase, and TNF-α.

However, the results were not as optimistic in a randomized double-blind placebo-controlled study that assessed the effects of sorafenib administered at 400 mg twice a day on HVPG in nine patients with cirrhosis and hepatocellular carcinoma[72].

The main drawback of tyrosine kinase inhibitors is hepatotoxicity. A study of possibilities of their selective delivery to target cells, in particular, HSC, seems to be a promising direction in solving this problem.

CONCLUSION

Advances in understanding the pathogenesis of PH in cirrhosis stimulated the development of new methods

Table 1 Drugs that can inhibit intrahepatic angiogenesis in portal hypertension

Ref.	Drugs	Experimental models	Effects
Liu *et al*[15], Qu *et al*[16], Wang *et al*[17], Thabut *et al*[18], Mejias *et al*[19]	Sorafenib	Biliary cirrhosis, non-alcoholic steatohepatitis, thioacetamide-, diethylnitrosamine-, dimethylnitrosamine-, and CCl_4-induced cirrhosis	Suppresses the Raf/MEK/ERK signaling pathway and blocks the signaling from the VEGFR, PDGFR, and SCFR; therefore, increases apoptosis and decreases inflammation, fibrogenesis, angiogenesis, and hepatic vascular resistance
Tugues *et al*[20], Majumder *et al*[21]	Sunitinib	CCl_4-induced cirrhosis and cell cultures (immortalized human activated HSC cell line, human HSC, and isolated primary human liver sinusoidal endothelial cells)	Blocks VEGFR1/2/3, PDGFR-α/β, FGFR, and SCFR; reduces HSC collagen synthesis, contractility, cellular migration, and SEC angiogenic capacity
Lin *et al*[22], Yang *et al*[23]	Brivanib	Biliary cirrhosis, non-alcoholic steatohepatitis	Inhibits VEGFR and FGFR; therefore, suppresses intrahepatic angiogenesis and portal hypertension, improves blood circulation, and hinders ascites formation
Miao *et al*[31], Marrone *et al*[32]	Simvastatin	CCl_4-induced cirrhosis and LX-2 cell line	Enhances KLF2, through which deactivates SEC and reduces the severity of fibrosis and associated angiogenesis
Zhu *et al*[35]	Rifaximin	Biliary cirrhosis	Downregulates bacterial lipopolysaccharide binding to TLR4; therefore, reduces the severity of fibrosis and associated angiogenesis
Liu *et al*[37], Liu *et al*[38]	Largazole	Human colorectal carcinoma cells (HCT116, HT29, and HCT15), human HSC, and CCl_4-induced cirrhosis	Suppresses the effects of CD34, VEGF, TGF-β1, and VEGFR2, blocking the main fibrogenic and angiogenic pathways
Michaelis *et al*[40]	Ribavirin	Human umbilical vein endothelial cells	Hinders angiogenesis by inhibiting inosine-5'-monophosphate dehydrogenase 1, tetrahydrobiopterin, NO, and cGMP

CCl_4: Carbon tetrachloride; VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet-derived growth factor receptor; SCFR: Stem cell growth factor receptor; FGFR: Fibroblast growth factor receptor; HSC: Hepatic stellate cells; SEC: Sinusoidal endothelial cells; KLF2: Krüppel-like factor 2; TLR4: Toll-like receptor 4; TGF-β1: Transforming growth factor beta 1; NO: Nitric oxide; cGMP: Cyclic guanosine monophosphate.

Table 2 Drugs that can inhibit extrahepatic angiogenesis in portal hypertension

Ref.	Drugs	Experimental models	Effects
Fernandez *et al*[46]	Rapamycin and glivec	Partial portal vein ligation	Downregulates VEGF, VEGFR2, CD31, PDGF, PDGFR-β, and α-SMA
Mejias *et al*[19]	Sorafenib	Partial portal vein ligation and CCl_4-induced cirrhosis	Blocks VEGF, PDGF, and Raf/MEK/ERK signaling pathway; therefore, reduces intraorgan and systemic blood flow, splanchnic neovascularization, portosystemic shunting, hepatic vascular resistance, and portal pressure
Woltering *et al*[49], Mejias *et al*[50]	Somatostatin and its synthetic analogs	Partial portal vein ligation	Reduces VEGF and CD31 expression, splanchnic neovascularization, and portosystemic collateral circulation by blocking SSTR2
Miternique-Grosse *et al*[55]	Spironolactone	Biliary cirrhosis	Suppresses the effects of aldosterone and the VEGF signal transduction pathway
Lee *et al*[58]	N-acetylcysteine	Biliary cirrhosis	Reduces oxidative stress, inflammatory cytokine levels, TNF-α, VEGF, VEGFR2, Ang1, CD31 expression, and suppresses Akt/eNOS/NO pathway
Hsu *et al*[61]	Bosentan and ambrisentan	Biliary cirrhosis	Block endothelin receptors and suppress iNOS, cyclooxygenase 2, VEGF, VEGFR2, and Akt signaling
Schwabl *et al*[64]	Pioglitazone	Biliary cirrhosis	Downregulates inflammatory genes and NF-κB expression, suppresses angiogenic and pro-inflammatory cytokines, chemokines, and growth factors (VEGF, PDGF, and PIGF)
Li *et al*[66]	Thalidomide	Biliary cirrhosis	Hinders TNF-α/interleukin-1β production and blocks the TNFα-VEGF-NOS-NO pathway
Hsu *et al*[67]	Catechins of *Camellia sinensis*	Biliary cirrhosis	Reduce HIF-1α expression, Akt signaling, and VEGF synthesis
Hsin *et al*[68]	2′-hydroxyflavonoid	Thioacetamide-induced liver cirrhosis	Downregulates apoptosis
Hsu *et al*[69]	Curcumin	Biliary cirrhosis	Suppresses VEGF, cyclooxygenase 2, and eNOS

CCl_4: Carbon tetrachloride; VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet-derived growth factor receptor; α-SMA: Alpha smooth muscle actin; SSTR2: Somatostatin receptor type 2; TNF-α: Tumor necrosis factor alpha; Ang1: Angiopoietin 1; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide; iNOS: Inducible nitric oxide synthase; NF-κB: Factor kappa-light-chain-enhancer of activated B cells; PIGF: Placental growth factor; HIF-1α: Hypoxia-inducible factor-1 alpha.

for its pharmacotherapy. Currently, the drugs of choice are nonselective β-blockers. Nevertheless, their use is not recommended during the subclinical stage of the disease, when the most justified treatment is etiotropic and pathogenetic and aimed at, for example, affecting fibro- and angiogenesis in the liver, as well as angiogenesis underlying the formation of portosystemic shunts. Etiogenic approach, as part of a complex correction of pathophysiological disorders that contribute to the development of PH, may be the key to

success in preventing related complications.

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