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MANAGEMENT OF CIRRHOTIC PATIENT (A CARDENAS AND P TANDON, SECTION EDITORS)

Future Pharmacological Therapies of Portal Hypertension

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Abstract

Purpose of Review To provide an overview of recent pharmacological treatments for portal hypertension evaluated in early clinical trials, with particular emphasis on the pathophysiological basis of their use.

Recent Findings In patients with compensated cirrhosis, even small decreases in portal pressure (as small as 1 mmHg) are associated with a lower probability of decompensation. In patients with decompensated cirrhosis, portal pressure "response" to non-selective beta-blocker (NSBB) therapy is associated with a lower mortality. When present, significant portal hypertension persists even after the elimination of the etiology of cirrhosis and this justifies the continued development of new drugs that target portal hypertension.

Summary Over several decades, we have gained great depth in the understanding of portal hypertension, its mechanisms and complications. NSBBs, which act by reducing portal venous inflow (an extrahepatic target), are effective in reducing portal pressure and have been the mainstay of therapy for portal hypertension in the last 35 years—being effective in preventing decompensation and variceal hemorrhage. However, because not all patients will have a sufficient response to NSBB and some may be intolerant to NSBB, alternative drugs or drugs that will augment the effect of NSBB on portal pressure are being tested in pre-clinical and early-clinical trials. Many of these drugs target more than one of the intrahepatic or extrahepatic mechanisms implicated in the pathogenesis of portal hypertension in cirrhosis. Out of these proposed therapies, statins have emerged as the most promising new pharmacological therapy for the treatment of portal hypertension.

Keywords Portal hypertension · Liver cirrhosis · Hepatic venous pressure gradient · Statins · Sinusoidal endothelial dysfunction · Liver fibrosis · Splanchnic vasodilation

Introduction

Cirrhosis, the final stage of chronic liver diseases, is an increasing cause of morbidity and mortality worldwide. According to recent data available, cirrhosis has a global annual mortality of 12.6M [1], with 34.2 thousands deaths in the USA [2] and is positioned among the 14 leading causes of death in the world.

Cirrhosis cannot be considered a single entity and is subclassified into two main clinical stages: compensated and decompensated [3, 4]. Decompensation in cirrhosis is defined by the development/presence of clinically overt complications (ascites, encephalopathy, variceal bleed, or jaundice) [3], and is the main determinant of death in cirrhosis [4, 5]. The median survival of a patient with compensated cirrhosis is greater than 12 years (as long as the patient remains in the compensated stage), whereas in the decompensated patient, it is below 2 years [6].

The main pathogenic substrate to decompensation is an increase in portal pressure (portal hypertension). This is based on studies performed in patients with cirrhosis in whom portal pressure and the degree of portal hypertension (PH) is determined indirectly by measuring the hepatic venous pressure gradient (HVPG), which is obtained by catheterization of one of the major hepatic veins and by subtracting the wedged (or balloon-occluded) minus the free hepatic venous pressure [7]. Normal HVPG is 3–5 mmHg. Most patients with compensated cirrhosis have an HVPG >5 mmHg but those with an

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HVPG ≥ 10 mmHg have a four-times higher risk of decompensation than patients with compensated cirrhosis who have not reached this threshold [8]. Accordingly, patients with compensated cirrhosis are currently sub-staged into those with mild PH (HVPG ≥ 5, < 10 mmHg) and those with clinically significant portal hypertension (CSPH = HVPG ≥ 10 mmHg) [9]. Patients with CSPH are not only at a higher risk of decompensation, and therefore death [10], but are also at a higher risk of development of varices and hepatocellular carcinoma [11, 12, 13••]. Clinically, a patient with cirrhosis who has varices (independent of size), portosystemic collaterals on imaging, or is decompensated has, by definition, CSPH.

In patients with compensated cirrhosis, the main goal of treatment is to prevent decompensation. HVPG "responders" to non-selective beta-blockers (NSBB) has been shown to prevent first variceal hemorrhage, development of ascites, and death [14, 15]. Definition of response has been based on threshold decreases in HVPG, the most commonly used being a decrease > 20% from baseline or to levels below 12 mmHg. However, recent data suggest that absolute reductions in HVPG may provide more granularity. Using data from the timolol study in which measures of HVPG were performed yearly for up to 8 years [11], joint modeling (combining Cox model and mixed effects model) showed that changes of only 1 mmHg in the HVPG are associated with 1.19-time increase or decrease in risk of decompensation or death [16]. In the setting of compensated cirrhosis, elimination of the etiological agent, e.g., use of direct-acting antivirals for hepatitis C (HCV), delays decompensation and may lead to a decrease in HVPG, particularly in early stages of cirrhosis (i.e., those with mild PH) [17]. However, CSPH persists in the majority of patients despite HCV elimination and therefore these patients continue to be at risk of decompensation and HCC [18, 19].

In patients with decompensated cirrhosis, the main goals of treatment are to prevent further decompensation and, mainly, to prevent death. As in compensated cirrhosis, patients with ascites who had bled from varices who are HVPG responders to NSBB have a lower risk of further decompensation and death [15, 20, 21].

It is clear, therefore, that reducing portal pressure in patients with cirrhosis and significant PH (compensated or decompensated) is associated with improved outcomes [3, 22].

Understanding the pathophysiology of PH, particularly the discovery of splanchnic vasodilatation and the hyperdynamic circulation as main contributors to CSPH, has led to the introduction of the vasoconstrictors (e.g., terlipressin, octreotide) for the treatment of acute variceal hemorrhage [23••] and the use of NSBB for the prophylaxis of variceal hemorrhage. For over 30 years, the use of NSBB has remained the mainstay of therapy for PH [24]. While NSBB have been shown to decrease variceal hemorrhage and death [25] as well as decompensation in patients with compensated cirrhosis and CSPH [26], not all patients experience a significant reduction in PP with NSBB, and some patients are unable to tolerate this treatment [27]. Therefore, new drugs that could be used in combination or in lieu of NSBB are necessary.

To promote the development of therapies for PH, the American Association for the Study of Liver Disease (AASLD) recently published a consensus that propose a framework for the design of clinical trials and prioritizing targets and therapies for PH. This consensus reviews the available therapies in preclinical and clinical phase for the treatment of PH [28••]. The reader should refer to the consensus to expand on the preclinical studies and for considerations regarding study design for potential drugs that may reduce portal pressure in compensated cirrhosis.

This review will (1) describe the known mechanisms of PH and point to the potential therapeutic targets; (2) summarize main candidate drugs associated with a reduction in portal pressure in patients with cirrhosis.

Pathophysiological Basis and Therapeutic Targets in Portal Hypertension

There are several mechanisms, both intra- and extra-hepatic involved in the development of PH in cirrhosis (Fig. 1).

Intrahepatic Mechanisms: Increased Resistance to Flow

Within the liver, increase in portal pressure is due to increased resistance to flow, which is secondary to (a) structural distortion of liver parenchyma, which include fibrosis, disruption of sinusoidal structure (e.g., nodular regeneration), and microthrombi in the hepatic circulation, and (b) functional or dynamic changes in the hepatic vascular tone (i.e., endothelial dysfunction and active vasoconstriction) [29•]. In patients with compensated cirrhosis and mild PH, the main mechanisms are intrahepatic. Therefore, both structural and functional abnormalities could be targeted at the compensated stage [28••].

a) Structural distortion of liver parenchyma includes fibrosis and replacement of healthy parenchyma by extracellular matrix, the histological hallmark of cirrhosis. Structural abnormalities account for 70% of the increased intrahepatic resistance. Treatment of the underlying etiology is key in patients with cirrhosis as regression to less advanced stages of liver fibrosis may occur as described after treatment of hepatitis B [30]. This may be particularly pertinent in patients with mild PH as these patients are more likely to have thin fibrous septa [31] and it is

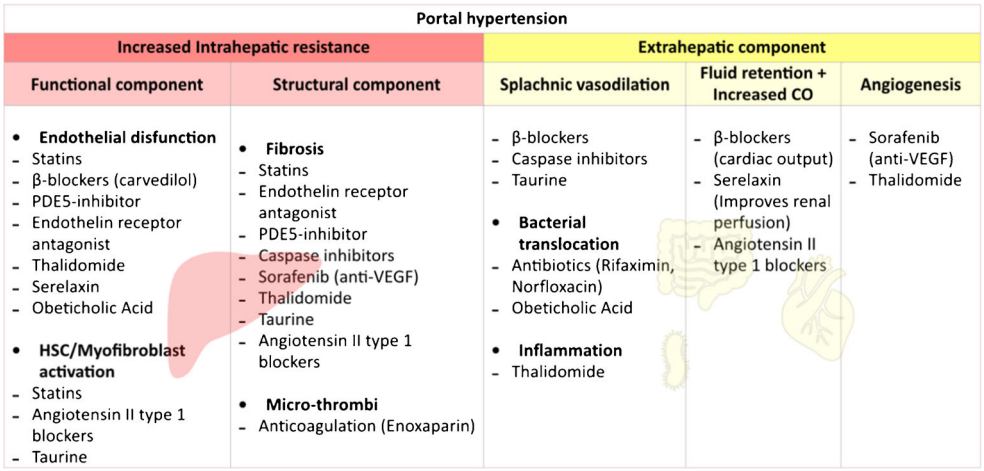

Fig. 1 Mechanisms contributing to portal hypertension and medications that target these mechanisms

conceivable that targeting fibrosis on them may delay progression to CSPH or even lead to regression to a non-cirrhotic stage [32].

Besides etiological therapies, several drugs that target a major mechanism implicated in early stages of hepatic fibrogenesis, that is, the activation and transition of hepatic stellate cells (HSCs) into proliferating, extracellular matrix-producing myofibroblasts are under investigation [33, 34]. The use of farsenoid X receptors (FXR) agonists [35], endothelin-A receptor blockers [36, 37], the amino acid taurine [38], and angiotensin II type 1 receptor blockers [39–44], are all strategies that decrease activation of HSCs [34, 45–49]. The inhibition of hepatocyte apoptosis, one important step leading to inflammation and fibrosis, is targeted by the pan-caspase inhibitor emricasan, and is also being investigated as a therapy for liver injury and PH [50–52].

Microthrombi in the hepatic circulation contribute to the structural changes related to increase resistance. Frequent thrombotic occlusions of small veins and sinusoids in cirrhosis lead to fibrosis and "parenchymal extinction," i.e., irreversible loss of contiguous hepatocytes and their replacement by fibrous tissue [53, 54]. Anticoagulation is a strategy under investigation that would target this pathway.

b) Functional resistance to flow, i.e., increased vascular tone, accounts for approximately 30% of vascular resistance [55]. These functional changes have been associated to sinusoidal endothelial dysfunction [29•], which is characterized by diminished production of nitric oxide (NO) through diminished expression or activation of the endothelial NO synthase (eNOS) [56, 57]. This intrahepatic vasoconstriction is augmented by an increase in vasoconstrictive molecules, such as endothelins, adrenergic hormones, and angiotensin that increase HSC contractility [58, 59]. Statins (see below) are the only drugs that ameliorate endothelial dysfunction in cirrhosis.

Carvedilol, a NSBB that is a recommended therapy for PH differs from traditional NSBB such as propranolol or nadolol (that act by decreasing portal flow as described below) by also having an α1-adrenergic blockade effect that will potentially lead to intrahepatic vasodilation. This effect may explain why carvedilol has a larger portal-hypotensive effect compared to traditional NSBB [23••]. However, while traditional NSBB have a mild effect on blood pressure, carvedilol at standard doses of 25–30 mg/day has been associated with hypotension and fluid and salt retention [60]. Therefore, doses above > 12.5 mg/d are not recommended in the treatment of PH and, in fact, its use should be discouraged in patients with ascites, unless systemic hypertension is also being targeted [61, 62].

Other vasodilating agents that have been tested in phase-2 trials that would target the increased dynamic resistance to flow include phosphodiesterase type 5 (PDE5) inhibitors [63–65] and endothelin receptor blockers [36, 37]. However, vasodilatation is not only intrahepatic but systemic leading to hypotension with potentially deleterious effects such as sodium retention and acute kidney injury.

Extrahepatic Mechanisms: Increased Flow

The extrahepatic mechanisms occur as a response to mild PH. They include splanchnic vasodilatation (due to an increase in nitric oxide synthesis by splanchnic vessels) and neoangiogenesis [66, 67]. Splanchnic (and systemic) vasodilatation lead to relative hypovolemia and activation of neurohumoral mechanisms that promote sodium and water retention, subsequent hypervolemia, increased cardiac output, and the development of a hyperdynamic circulatory state that further increases portal flow, leading to CSPH [29•, 68•].

The increased portal flow is a target of NSBBs (propranolol, nadolol, and carvedilol), which are the established therapy for the treatment of PH. NSBBs counteract the increase in cardiac output via β1 blockade and cause splanchnic

vasoconstriction via β2-receptor blockade [69]. NSBB have proven to be effective in reducing portal pressure and preventing complications and mortality at most stages of cirrhosis, from CSPH with varices, to patients decompensated from variceal bleeding [23••, 25, 70]. However, in patients with mild PH when the hyperdynamic circulatory state is not yet well established, NSBB will be ineffective [11, 71]. In a recent meta-analysis, patients with cirrhosis, with or without ascites, who respond to NSBB by decreasing HVPG > 10% or 20% from baseline or by decreasing HVPG to < 12 mmHg, were shown to have lower rates of decompensating events as well as a lower death/transplant rates [15]. However, this study also showed that only 50% of patients without ascites, and 42% of patients with ascites demonstrated this response to NSBB [15]. Importantly, in a recent placebo-controlled RCT that included patients with compensated cirrhosis and CSPH with no or small varices, NSBB were associated with a significant decrease in the probability of decompensation/death [26]. This is the first study that shows an effect of a portal-pressure reducing therapy in preventing cirrhosis decompensation.

Bacterial translocation and inflammation are important drivers of the hyperdynamic circulatory state [72]. Several markers of systemic inflammation are elevated in advanced cirrhosis, including C-reactive protein (CRP) and interleukin 6 (IL-6), and correlate with more severe stages of cirrhosis and mortality [68•, 73]. Thalidomide targets this inflammatory pathway through inhibition of tumor necrosis factor (TNF) production and is being tested in the treatment of PH [74–76]. The use of poorly absorbed antibiotics, as a means to selective intestinal decontamination and decrease in bacterial translocation, is also being tested as a tool to decrease PH through attenuating inflammation.

Lastly, the development of collateral vessels, a major component of the hyperdynamic state of cirrhosis [66, 77], has been targeted in small trials evaluating the use of sorafenib and its effects in PH [78, 79].

Potential Future Therapies for Treatment of Portal Hypertension

In this section, results from the most relevant studies exploring the effect of the abovementioned therapies for the treatment of PH will be summarized. A description of each individual study is specified in Table 1.

Drugs that Act Mainly on Intrahepatic Component

Statins This is the most investigated and perhaps the most promising future therapy for PH. Statins are inhibitors of the 3-hydroxyl-methyl coenzyme A reductase (HMG-CoA-R) and are recommended for the treatment of hyperlipidemia. However, statins have pleiotropic effects that go beyond their cholesterol-lowering effect. These effects include decrease of inflammation and oxidative stress at the vessel wall, decreased thrombosis, and increase nitric (NO) production in endothelial cells through the inhibition of the small G-proteins Rho and Rac [88, 89]. Statins increase NO production through increased synthesis and phosphorylation of the eNOS in the liver, targeting endothelial dysfunction [56, 90, 91]. Early use of statins has also been shown to attenuate liver fibrosis in animal models at early stages of cirrhosis, through decrease activation of HSCs; this effect has been observed by different statins such as atorvastatin [92] or simvastatin [93], suggesting a class effect.

An initial exploratory study in a small number of patients with cirrhosis and an HVPG ≥ 12 mmHg at baseline showed that a single dose of 40 mg of simvastatin significantly decreased hepatic resistance by 15%, allowing an increase in hepatic blood flow, without significant changes in HVPG and without changes in systemic hemodynamics. Nitric oxide levels significantly increased at hepatic veins, but not at peripheral veins [80].

A proof-of-concept RCT of 59 patients with cirrhosis and HVPG ≥ 12 mmHg, assigned to 40 mg daily vs. placebo tested the effectiveness of statins in treating PH. After 1 month of treatment, patients assigned to simvastatin had a significant decrease in HVPG (8.3% decrease), regardless of concurrent use of β-blockers. The study confirmed an improvement in liver perfusion as demonstrated by an increase in the clearance of indocyanine green [81]. These results go in line with a smaller RCT reported as an abstract that showed that in patients with CSPH and high-risk varices who were non-responders to traditional NSBB, the addition of simvastatin 40 mg/d to carvedilol improved the clinical efficacy of treatment (decrease in HVPG) compared to carvedilol alone at 1 month [94]. In a smaller trial including 24 patients assigned to simvastatin 40 mg for 3 months vs. placebo, simvastatin was associated with significant decrease in HVPG. In this study, the magnitude of effect was larger in patients with baseline HVPG ≥ 12 mmHg and in subjects with prior history of variceal bleed or with known medium to large varices [95].

The effect of statins in preventing decompensation was explored in a propensity-matched retrospective study that used a large database of US veterans with HCV cirrhosis, demonstrating that statin users (compared to non-users) had a significantly lower risk of developing decompensation (with significantly lower rates of variceal hemorrhage and ascites) and a significantly lower risk of death [96].

Finally, the effectiveness of statins in the prevention of variceal rebleeding was tested in a RCT, where 158 patients with cirrhosis who had recovered from an episode of variceal hemorrhage were randomized to 40 mg of simvastatin in addition to the standard of care (variceal ligation and NSBB) vs. standard of care and placebo. In this study, simvastatin failed

Table 1 Summary of trials for novel pharmacological therapies in portal hypertension

Drug group therapy	Author (year)	Study description	Effect on HVPG	Other markers of liver health improvement	AEs/deleterious signal
Drugs with intrahepatic action					
Statins					
•Simvastatin 40 mg once	Zafra, 2004 [80]	[two different protocols all subjects with HVPG ≥ 12] (1) $n = 13$ ICG clearance after single dose. (2) $n = 17$ randomized to placebo or simvastatin with HVPG measured in both groups, before and after a meal.	Simvastatin attenuated the postprandial increase in HVPG (mean peak increase, 10% vs. 21%; $P < 0.01$)	Improved hepatic perfusion by ICG clearance. Increased NO production in hepatic vein. Decreased sinusoidal resistance.	n/r
•Simvastatin 40 mg QD	Abraldes, 2009 [81]	$n = 59$, cirrhosis HVPG ≥ 12 mmHg, assigned to simvastatin vs placebo for one month. HVPG measured at baseline and end of study.	Subjects assigned to simvastatin had a significant decrease in HVPG (8.3% drop on average), regardless of concurrent use of β-blockers	Improved ICG clearance.	2 subjects in treatment group had > 2-fold increase in CK at end of Rx.
•Simvastatin 40 mg QD plus standard of care, vs placebo plus standard of care.	Abraldes, 2016 [82••]	Phase-3 clinical trial $n = 158$, cirrhosis decompensated by variceal bleed, randomized to simvastatin plus standard of care (variceal ligation and NSBB)	n/r	Simvastatin did not decreased rate of rebleeding. Simvastatin had an impact in survival.	1 pt. on simvastatin had > 3-fold increase in transaminases 2 episodes of rhabdomyolysis in Rx.
PDE5 inhibitors					
•Sildenafil 25 mg once	Tandon, 2010 [65]	$n = 12$, compensated cirrhosis and PH. With HVPG and systemic hemodynamics measured at every 30 min for 1 ½ hours.	No effect on HVPG	n/r	Hypotension.
•Udenafil 12.5, 25, 50, 75, or 100 mg/day	Kreisel, 2015 [64]	$n = 36$, liver cirrhosis and CP A or B, with HVPG ≥ 12 mmHg. Received therapy for 1 week.	Combination of the 75 and 100 mg groups, showed significant 19.9% reduction on HVPG.	n/r	High dose group MAP decreased ~6%
•Vardenafil 10 mg once.	Deibert, 2006 [63]	$n = 36$, 18 healthy and 18 CP A subjects. 5 patients with cirrhosis had HVPG measurements.	In patients with HVPG measured, 4/5 had decrease in HVPG.	Improved hepatic flow	n/r
Angiotensin II type I receptor blockers					
•Candesartan 8 mg QD vs. no treatment.	Debernardi, 2007 [41]	$n = 47$, compensated cirrhosis randomized to candesartan or no treatment for 1 year.	On average 8.4% decrease in HVPG (13.2 from 14.5 mmHg at BL)	Decreased levels of hyaluronic acid. Stable GFR	Decrease in systemic BP
•Olmesartan 10 mg QD	Hidaka, 2007 [43]	$n = 18$, cirrhosis with recent esophageal bleeding (mean HVPG20.4 mmHg) vs controls. Treated for 2 weeks	Olmesartan reduced HVPG 16.8%. (20.3 to 17.3 mmHg average). 33% of patient had > 20% reduction.	n/r	Decreased in MAP 13%.
•Olmesartan 20-40 mg QD vs no treatment for 1 year	Hidaka, 2011 [83]	$n = 48$, cirrhosis mostly HCV and CP class A, HVPG 15.9 mmHg average.	HVPG reduction of 12.9% at one year. 25% of patient had > 20% reduction.	TGF-beta1 (pro-fibrogenic mediator of angiotensin).	MAP reduction 9.8%. Hypotension requiring discontinuation in1 pt.
•Losartan 25 mg QD vs. propranolol	Castano, 2003 [39]	$n = 27$, compensated cirrhosis, average HVP 16.4 mmHg.	HVPG reduction (from 15.6 to 11.8 mmHg). Eight patients had > 20% reduction. Best response was	n/r	n/r

Table 1 (continued)

Drug group therapy	Author (year)	Study description	Effect on HVPG	Other markers of liver health improvement	AEs/deleterious signal
			in pt. with very elevated HVPG (≥ 16 mmHg).		
•Losartan 25 mg QD vs. propranolol 40 mg BID	De, 2003 [40]	*n* = 39, cirrhosis, mostly EtOH, and known EV or HVPG ≥ 12 mmHg (~ 50% w/ Hx of decompensation), Mean CPS 9. Two wks of Rx	Subjects in Losartan had 26% reduction in HVPG (19.2 to 14.1 mmHg) vs. 14.5% for those in propranolol. Not statistically significant. 42% of pts. in losartan reach HVPG≤12 mmHg	n/r	One subject developed systolic BP < 80, required titration of dose.
•Losartan 50 mg QD (If tolerated) vs. propranolol 160 mg BID (if tolerated)	Gonzalez-Abraldes, 2001 [42]	*n* = 40, cirrhosis and history of EV bleeding. (Mean CPS 7), mean HVPG 19.1 mmHg. Treated for 6 weeks.	No significant change was seen in Losartan group (decrease 2%HVPG on average)	Propranolol decreased CO.	Losartan decreased MAP significantly, worse in pt. with CP class C.
•Irbesartan 300 mg QD + propranolol 20 mg BID vs. placebo + Propranolol	Schepke, 2008 [44]	*n* = 32, cirrhosis mean HVPG 18.7 mmHg. 8 weeks of treatment.	Addition of Irbesartan to propranolol had no effect on HVPG	Increase sodium excretion.	n/r
Thalidomide					
•Thalidomide 200 mg/day vs. pentoxifylline	Austin, 2004 [74]	*n* = 12, EtOH cirrhosis w/ EV, effect on HVPG at 2 wks. 6 patients were randomized to thalidomide.	Thalidomide reduced HVPG from 19.7 to 12.2 mmHg. 5/6 subjects decrease > 20% HVPG	Reduced production of TNF-alpha ex-vivo experiments.	Somnolence.
Endothelin-A (ET-A) receptor antagonist					
•BQ-123 (selective ET-A), or BQ-788 (selective ET-B), or placebo	Tripathi, 2006 [37]	*n* = 16, cirrhosis and PH, average CPS 6.2,	Compared to placebo, BQ-123 and BQ-788 had no effect on HVPG.	n/r	Decreased systemic BP.
•Ambrisentan 5 or 10 mg PO; BQ-123 2K nnmol/L	Zipprich, 2016 [36]	*n* = 26 cirrhosis, Child B-C. 14pts received ambrisentan PO and HVPG measured 90mins after Rx. *N* = 12 infusion of BQ-123 into hepatic artery.	Ambrisentan caused significant decrease HVPG of 5.4%, higher with higher dose. BQ-123Infusion caused 18% decrease.	No changes in systemic BP.	n/r
Drugs with extrahepatic action					
Antibiotics					
•Rifaximin1200mg QD	Kalambokis, 2012 [84]	*n* = 13, EtOH cirrhosis with ascites, CP class A-B. Treated for 4 weeks.	n/r	Decrease CO. Improved GFR.	n/r
•Rifaximin 550 mg BID vs. placebo	Kimer, 2017 [85]	*n* = 54, cirrhosis with ascites. HVPG measured baseline and after 4 weeks of treatment.	No effect on HVPG with Rx (16.8 BL to 16.6 mmHg).	No effect on CO, GFR, or vasoactive hormones.	n/r
•Norfloxacine 400 mg BID vs placebo	Rasaratnam, 2003 [86]	*n* = 14, RCT EtOH cirrhosis and 14 matched controls.	HVPG reduction 2.43 mmHg on average (did not reach significance)	Reduced endotoxin levels. Increased vascular resistance & MAP.	n/r
Drugs with intra and extrahepatic action					
Caspase inhibitors					
•Emricasan 25 mg BID	Garcia-Tsao, 2018 [52]	*n* = 23, compensated cirrhosis and PH (HVPG > 5 mmHg, *n* = 12 with	Overall no significant change. In subgroup analysis, those with	Improved transaminases.	Fatigue, headache, peripheral edema.

Table 1 (continued)

Drug group therapy	Author (year)	Study description	Effect on HVPG	Other markers of liver health improvement	AEs/deleterious signal
		HVPG ≥ 12 mmHg), mostly child-A. Multicenter, open label study. HVPG after 28 days Rx.	HVPG > 12 mmHg had significant decrease of 3.7 mmHg on average.		
FXR-agonist					
• Obeticholic acid 10 or 25 mg QD	Moorkerjee, 2014 [35]	$n = 25$, EtOH cirrhosis and PH. HVPG 7–12 days of Rx.	9/16 pt. decreased HVPG < 12 mmHg. In all subject no significant decrease 16 to 13.8 mmHg ($P = 0.07$)	No change in LFT's or measured cytokines.	Pruritus in high-dose group.
Sorafenib					
• Sorafenib 400 mg BID	Pintes, 2012 [79]	$n = 13$, cirrhosis and HCC not eligible for curative Rx. CP A or B. Only 11 Pts had HVPG > 5 mmHg. Treated for 2 weeks.	Of 11 subjects with PH, 36% had ≥20% decrease in HVPG.	Significant improve in MAP. Decreased mRNA of VEGF, TNF-alpha.	n/r
• Sorafenib 400 mg BID vs. placebo	Garcia-Tsao, 2015 [78]	$n = 10$, RCT of HCV Cirrhosis w/ HVPG > 5 mmHg and unresectable HCC with ablation.	No evidence that Sorafenib improves HVPG.	n/r	Diarrhea, abd. Pain, nausea, fatigue.
Taurine					
• Taurine 6 g/day vs. placebo	Schwarzer, 2018 [38]	$n = 22$, 64% child-B, effect of taurine on HVPG at 28 days	On average 12% reduction (20 to 18 mmHg)	No effect on systemic hemodynamics.	Gastrointestinal discomfort.
Serelaxin				Better renal perfussion	
• Serelaxin IV 30 μg/kg/day vs. terlipressin 2 mg	Snowdown, 2017 [87]	$n = 38$, EtOH cirrhosis and PH. Measured renal blood flow by PC-MRA at 2 h	n/r	Improvement of renal perfusion. Non-significant increase in portal vein and hepatic artery flow.	No adverse effects reported.

EV, esophageal varices; n/r, not reported; CP, Child-Pugh; Rx, therapy; CO, cardiac output; MAP, mean arterial pressure

to decrease the rate of rebleeding; however, it showed an improvement in survival mostly in patients with child class A and B [82••]. The increase in survival was determined by a decrease in mortality derived from rebleeding and infections.

The adverse events (AE) reported in the phase-2 and phase-3 trials of statins indicate a good safety profile of this medication. However, patients with advanced liver disease, CP scores > 13, or with acute kidney injury have been excluded from most of these trials. Perhaps one of the most concerning AE of the use of statins is the development of rhabdomyolysis. In the study by Abraldes et al. [82••], 2 out of 70 subjects (3%) receiving 40 mg of simvastatin daily developed rhabdomyolysis, which would rarely happen at this dose in general population (0.1% using 80 mg daily) [97]; both subjects had severely deteriorated liver function. The safety of two doses of simvastatin (associated to rifaximin) in patients with decompensated cirrhosis was recently tested in a placebo-controlled RCT showing that 40 mg of simvastatin was associated to higher AST and ALT, as well as higher creatinine-kinase levels compared to 20 mg or placebo; with clinically significant rhabdomyolysis reported in 3 of 16 (19%) patients randomized to 40 mg while this adverse event did not occur in patients randomized to 20 mg or to placebo [98]. Therefore, in patients with decompensated cirrhosis, doses of simvastatin 40 mg or higher should not be used and should probably be used cautiously in patients with compensated cirrhosis.

PDE5 Inhibitors In early-clinical trials, PDE5 inhibitors have shown mixed results in HVPG. The use of sildenafil in patients with compensated cirrhosis and PH was not associated with decrease in portal pressure [65], whereas udenafil and vardenafil showed a positive effect on HVPG [63, 64], and an ongoing phase-2 RCT is set to further investigate the effects of the vardenafil (NCT02344823). Hypotension, however, will be a limiting factor in their use as a significant decrease in MAP was reported with both sildenafil and udenafil (Table 1).

Angiotensin II Type 1 Receptor Blockers The renin-angiotensin axis contributes to PH at different levels. There is evidence that angiotensin is a mediator of mesenteric vasodilation in cirrhosis through the angiotensin converting enzyme-2 (ACE2) alternative pathway [99], and there is also evidence that the renin-angiotensin system, through angiotensin II type 1 receptor activation of HSCs, contributes to fibrogenesis and increased hepatic resistance in cirrhosis [58]. Several studies have explored the effect of different angiotensin II type 1 receptor blockers in HVPG (Table 1) with mixed results. Some of the studies reported a significant decrease in HVPG [39–43, 83]. However, as for any drug that causes vasodilation, a potentially deleterious reduction in systemic arterial pressure has been frequent on these studies and appears to be worse in patients with advanced stages of cirrhosis [42].

Thalidomide Thalidomide is an immunomodulatory drug that inhibits TNF-alpha pathway, thus decreasing inflammation [75, 76]. A small study of 12 patients with alcohol-related cirrhosis and CSPH, evaluated the effect to thalidomide on HVPG after 2 weeks of treatment; this study reported a reduction in portal pressure from 19.7 to 12.2 mmHg on average, and 5 out of 6 patients had > 20% reduction in HVPG [74]. Somnolence was the main AE reported on this trial, and no change in systemic arterial pressure was reported.

Endothelin Receptor Blockers As mentioned above, endothelins play a role in endothelial dysfunction, and they also appear to promote activation of HSCs [34] and liver fibrosis. Ambrisentan, an ET-A receptor blocker showed a dose-dependent decrease in HVPG in a pilot study in subjects with cirrhosis without changes in systemic blood pressure [36]. In contrast, BQ-123 (selective ET-A) and BQ-788 (selective ET-B) had no effect on HVPG but did show a potentially deleterious significant decrease in systemic blood pressure [37].

Drugs that Act Mainly in Extrahepatic Component

Selective Intestinal Decontamination Given the role of bacterial translocation in the perpetuation of inflammation in cirrhosis, poorly absorbed antibiotics have been tested as a therapy for PH showing mixed results. A small trial of rifaximin in 13 patients with alcohol-related cirrhosis decompensated by ascites, showed a decrease in cardiac output, increased vascular resistance and improvement of eGFR, as surrogates of improvement in the hyperdynamic state (no HVPG was measured) [84]. However, a more recent and larger trial, including 54 subjects with ascites, failed to replicate the beneficial effects of 1 month of rifaximin on hemodynamics with no changes in HVPG [85]. Another study evaluating norfloxacin failed to show an improvement in HVPG but showed improvement in MAP, increased vascular resistance and reduced endotoxin levels [86]. In post-hoc analysis of a recently published RCT of 291 patients with Child-Pugh class C cirrhosis, long term use of norfloxacin was associated with increased survival in a subset of subjects with low ascites protein (< 15 g/L) [100].

Intra- and Extrahepatic Action

Anticoagulation Anticoagulation has shown to reduce portal pressure in animal models [101]. In human cirrhosis, a prospective RCT of 75 patients with hepatitis-B cirrhosis, use of low molecular weight heparin (LMWH) was associated with improved liver chemistries, lower fibrosis markers (collagen), and improved portal vein blood flow by radiological assessment [102]. The interim results of a phase-2 trial (ISRCTN12504151) showed that one-year warfarin use

reduced liver fibrosis in liver transplant recipients with recurrent HCV infection [103]. The best evidence of the potential benefits of anticoagulation comes from a randomized open-label study that included 70 patients with decompensated cirrhosis without portal vein thrombosis that showed that patients who were assigned to enoxaparin for 1 year had a lower incidence, not only of portal vein thrombosis (0 vs 17% at 1 year) but also of further decompensation (12% vs 59% at 1 year) and death compared to no enoxaparin treatment [104]. An ongoing phase-3 RCT, CIRROXABAN (NCT02643212), aims to evaluate the effect of rivaroxaban in patients with cirrhosis and CSPH on decompensation and transplant-free survival at 24 months; as a secondary outcome, it is expected that this study will report results of anticoagulation on HVPG at 1 year.

Caspase Inhibitors The pan-caspase inhibitor emricasan (IDN-6556) decreases hepatocyte apoptosis, inflammation, and liver fibrosis in animal models of liver injury [50, 51]. In an open-label proof of concept trial in 24 patients with cirrhosis and PH, post-hoc analysis showed that 4-week course of emricasan was associated with a significant reduction in HVPG only in a subgroup of patients with baseline HVPG ≥ 12 [52]. A recently completed clinical trial (NCT02960204) aims to evaluate the effect of three different doses of emricasan on HVPG (5 mg, 25 mg, or 50 mg twice daily) in patients with NASH cirrhosis and an HVPG > 12 mmHg. In other phase-2 trials, emricasan showed improvement in INR and total bilirubin in a subset of cirrhotic patients with MELD ≥ 15 [105], as well as decrease in transaminases in subjects with NAFLD [106] and in subjects with chronic HCV infection [107]. The safety profile of emricasan in these trials was acceptable and adverse effects did not include hypotension.

FXR Agonist Obeticholic acid, an FXR agonist that targets hepatic fibrosis, as well as inflammation pathways [45, 46], has been evaluated in a proof-of-concept trial for the treatment of PH. The study included 23 patients with alcohol-induced cirrhosis and PH, who were randomized to 10 or 35 mg of obeticholic acid daily. Sixteen patients had HVPG measurements at baseline and after 1 week of treatment. No significant changes in portal pressure were shown; however, 9/16 participants were labeled as HVPG responders demonstrating a > 15% reduction from baseline or a reduction to < 12 mmHg after treatment [35].

Taurine Taurine, among other potential effects, inhibits HSC activation, which might lead to reduction in portal pressure [49]. This concept has been tested in a single pilot study where 22 patients, mostly decompensated cirrhosis, baseline HVPG ≥ 12 mmHg, were randomized to 6 g of taurine daily vs. placebo. Subjects assigned to taurine had a statistically significant reduction in HVPG, average 12% (~ 2 mmHg) at 4 weeks. Taurine was well tolerated; with gastrointestinal discomfort and fatigue being the only reported adverse effects and no changes in systemic hemodynamic parameters [38].

Sorafenib Angiogenesis of collateral vessels have been targeted by sorafenib, a tyrosine kinase inhibitor, in subjects with cirrhosis and HCC. In a first study including 13 patients with PH, not eligible for curative therapy of HCC, the use of sorafenib was associated with decrease in HVPG ≥ 20% in 4/11 patients at 2 weeks of treatment [79]. This effect, however, was not confirmed on another small trial including patients with HCV cirrhosis [78].

Conclusions

Portal hypertension is the main consequence of cirrhosis and is responsible for most of its complications. In fact, reducing portal pressure, both in patients with compensated and decompensated cirrhosis, has been shown to be associated with an improvement in important clinical outcomes including variceal hemorrhage, decompensation (early and late), and death. Therefore, reducing portal pressure is an important goal in the management of cirrhosis and has been based on the use of NSBB.

Increasing knowledge regarding the pathophysiology of PH has led to the identification of targets for potential new drugs that would augment the effect of NSBB or could be used as substitutes for NSBB (particularly in patients whose portal pressure does not decrease in response to NSBB). Most of the targets are intrahepatic but a combination of drugs that would target several intrahepatic and/or extrahepatic mechanisms would be ideal. Targets will differ depending on the stage of cirrhosis and the degree of portal hypertension and this should also be taken into consideration in the design of proof-of-concept studies.

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Compliance with Ethical Standards

Conflicts of Interest Guadalupe Garcia-Tsao participated in and is the first author of the open-label study on the effect of emricasan on hepatic venous pressure gradient (sponsored by Conatus). Guadalupe Garcia-Tsao reports personal fees from Conatus, grants and personal fees from Intercept, personal fees from Abbvie, personal fees from Biovie, personal fees from Enterome, personal fees from Grifols, personal fees from Galectin, outside the submitted work. Guillermo Ortiz declares no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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