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Review

REVIEW

Novel treatment options for portal hypertension

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Abstract

Portal hypertension is most frequently associated with cirrhosis and is a major driver for associated complications, such as variceal bleeding, ascites or hepatic encephalopathy. As such, clinically significant portal hypertension forms the prelude to decompensation and impacts significantly on the prognosis of patients with liver cirrhosis. At present, non-selective β-blockers, vasopressin analogues and somatostatin analogues are the mainstay of treatment but these strategies are far from satisfactory and only target splanchnic hyperemia. In contrast, safe and reliable strategies to reduce the increased intrahepatic resistance in cirrhotic patients still represent a pending issue. In recent years, several preclinical and clinical trials have focused on this latter component and other therapeutic avenues. In this review, we highlight novel data in this context and address potentially interesting therapeutic options for the future.

Key words: portal hypertension, hepatic venous pressure gradient, non-selective β-blockers, nitric oxide, angiogenesis, statins, farnesoid X receptor, renin–angiotensin–aldosterone

Introduction

Portal hypertension (PHT) is most commonly observed in patients with liver cirrhosis and is a major driver for associated complications, such as variceal bleeding, ascites or hepatic encephalopathy. Current PHT treatment strategies orientate on the existence and characterization of oesophageal varices, which strongly correlate with the hepatic venous pressure gradient (HVPG)—the gold standard for quantification of PHT. For prevention of variceal bleeding, oral non-selective beta blockers (NSBBs) are used, while, in acute bleeding situations, intravenous somatostatin, octreotide or terlipressin are available [1]. These drugs aim to decrease portal pressure; however, not all patients achieve a haemodynamic response, which is defined by a HVPG decrease >10% of baseline. Thus, current research intensively seeks new treatment options for PHT. Most experimental strategies aim at structural (liver fibrosis) and/or dynamic (endothelial dysfunction, hyperdynamic circulation) factors, which contribute to the severity of PHT. In this review, we summarize close to 100 different pharmacotherapies and their potential for future use in PHT.

Adrenoceptor drugs

The dynamic component of PHT is attributed to an increase in splanchnic arterial vasodilation and intrahepatic vascular resistance, which is at least partly mediated via adrenergic receptors. The established therapy with beta blockers counteracts the increased cardiac output (via β1) and substantially increases splanchnic resistance (via β2), which together reduces portal pressure [2,3]. Furthermore, α-receptor antagonism has been shown to additionally reduce intrahepatic resistance.

While there exists a plethora of beta-blocking agents, only a few NSBBs (propranolol, nadolol and carvedilol) are currently

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recommended for the treatment of PHT [1]. Notably, selective β1 blockade might even increase portal pressure, which has been shown for nebivolol in experimental cirrhosis [4]. On the other hand, additional α-receptor antagonism supports the NSBB-mediated decrease in HVPG. This has been demonstrated in clinical studies by the use of carvedilol (combined non-selective β and α1-blockade) [5–7] or by add-on therapy with the α1-antagonist prazosin [8,9].

Yet, according to a meta-analysis, haemodynamic response rates to NSBBs are only 46% [10]. Furthermore, beta-blocker therapy increases the risk of arterial hypotension, which is especially of concern when combined with α-antagonism (e.g. carvedilol) and in decompensated patients, where NSBB therapy might be even detrimental [2,11]. Thus, research aims to refine adrenoceptor pharmacotherapy.

In experimental cholestatic cirrhosis, short-term therapy with the α2 antagonist BRL44408 significantly decreased portal pressure and did not alter systemic haemodynamics even without NSBB cotherapy, which, however, has been published in only two abstracts so far [12,13].

While NSBB effects are mediated via β1 and β2 adrenoceptors, recent studies also shed light upon the lesser known β3 adrenoceptor, which is up-regulated in experimental and human cirrhosis. Stimulation of β3 adrenoceptors leads to relaxation of hepatic stellate cells (HSCs) and intrahepatic vasodilation via activation of the adenylyl cyclase and by inhibition of Rho-kinase. Accordingly, in cirrhotic rodent models, two studies measured significant declines in portal pressure after treatment with the β3 agonists CGP12177A and SR58611A, respectively [14,15].

Improving adrenergic vascular contractility in the splanchnic area can also be achieved by neuropeptide Y, which seems to be especially effective in PHT [16,17]. Accordingly, treatment with neuropeptide Y in cirrhotic rats translated into a significant amelioration of the portal hypertensive syndrome and PHT without changing mean arterial pressure [18]. In line, also administration of zolmitriptan, which mediates mesenteric vasoconstriction not via beta blockade, but via the 5-HT1 receptor, dose-dependently reduced portal pressure. Although this portal hypotensive effect was of short duration, co-administration with NSBBs synergistically prolonged and enhanced the decrease in portal pressure [19].

However, none of these approaches has yet been tested in humans and thus they remain experimental.

Nitric oxide

Imbalance of the potent vasodilator nitric oxide (NO) is a hallmark in the pathophysiology of PHT and sinusoidal endothelial dysfunction [20]. Lack of intrahepatic NO is responsible for increased intrahepatic resistance, while abundance of NO in the splanchnic area promotes portal inflow. Hence, targeting tissue-specific NO availability is a compelling treatment strategy, but systemic side effects (arterial hypotension) have to be scrutinized.

Historically, the NO donor isosorbide mononitrate has been used for the treatment of PHT [21], but is now excluded in most recent guidelines due to missing benefit [22]. Approaches of using a hepatospecific NO donor (NCX-1000) seemed promising in animal studies [23], but failed to reduce portal pressure in a human randomized–controlled trial (RCT) [24]. In a more recent trial, NO-releasing nanoparticles coated with vitamin A were used to specifically cause an intrahepatic vasodilation. In bile duct ligated (BDL) rats, these nanoparticles significantly decreased portal pressure without affecting mean arterial pressure [25].

Apart from affecting NO availability, also pharmacotherapies along the NO pathway have been successfully tested. NO is produced by NO synthases (NOS), which depend on the cofactor tetrahydrobiopterin. Hence, approaches of increasing NO production with the NOS transcription enhancer AVE 9488 or by supplementation of tetrahydrobiopterin were successful in reducing portal pressure and improving endothelial dysfunction in cirrhotic rat models [26–28]. However, in a human RCT, two weeks of sapropterin treatment had no effects on HVPG [29].

NO-induced vasorelaxation is mediated via cyclic guanosine monophosphate (cGMP), which is produced by the soluble guanylate cyclase (sGC) and degraded via phosphodiesterases (PDE). Hence, inhibitors of the PDE5 have been intensively tested in the setting of cirrhosis. Already, in healthy rats, PDE5 inhibition decreased intrahepatic resistance, and increased hepatic parenchymal and hepatic arterial flow, which resulted in a trend towards decreased portal pressure [30]. In BDL rats, acute infusions of sildenafil had no beneficial effects on portal pressure [31], whereas a weeklong therapy increased sinusoidal flow and decreased portal pressure [32]. In line, chronic udenafil treatment decreased portal pressure in BDL rats and furthermore exhibited antifibrotic effects [33].

Similarly, in cirrhotic patients, acute sildenafil administration decreased hepatic sinusoidal resistance but did not change HVPG [34–36], while one week of udenafil treatment caused a significant and dose-dependent HVPG decrease [37]. The PDE5 inhibitor vardenafil decreased HVPG in a pilot trial in four out of five patients after one hour [38] and its long-term effects on HVPG are currently being tested in a RCT [39].

More recently, sGC activators were investigated in experimental cirrhosis as antifibrotic effects and recovery of sinusoidal architecture have been described in cirrhotic animals [40,41]. A first report (*published as an abstract*) showed that chronic treatment with riociguat significantly decreased portal pressure in two rat models of biliary and toxic liver cirrhosis [42].

Vasoconstrictors

Instead of enforcing intrahepatic vasodilation, an alternative treatment strategy for PHT is to evade intrahepatic vasoconstriction. Thus, endothelin (ET) and urotensin are the focus of current research.

ET is a potent vasoconstrictor, which contributes to intrahepatic endothelial dysfunction and furthermore promotes liver fibrosis. In cirrhotic animals, acute and chronic ET-receptor antagonism (ET-A: Ambrisentan, BQ-123, A-147627, LU-135252; ET-B: BQ-788, A-192621; ET-AB: Bosentan, A-182086, SB209670) significantly decreased portal pressure; however, studies diverge about which receptor is responsible for the decrease in portal pressure [43–48]. Furthermore, these studies observed improvements in sinusoidal integrity and amelioration of liver fibrosis in animals treated with ET-receptor antagonists. While a small human study (*published as an abstract*) showed that administration of ET-A blocker (BQ-123 or Ambrisentan) caused a significant decrease in HVPG [49], two RCTs showed no effect on HVPG in cirrhotic patients after acute infusions with selective (BQ-123, BQ-788) or unselective (Tezosentan) ET antagonists [50,51]. Two RCTs investigating macitentan [52] or ambrisentan [53] in patients with portopulmonary hypertension are currently ongoing.

Urotensin is a rather newly described peptide, which is also a strong vasoconstrictor. Indeed, urotensin levels correlate with HVPG [54] and, in experimental models, the urotensin antagonist palosuran significantly decreased portal pressure without affecting mean arterial pressure via an increase in splanchnic resistance by affecting RhoA and NO pathways [55]. However, currently there are no human studies on urotensin antagonists.

Inflammation and bacterial translocation

Inflammation is the natural response for distress and facilitates the first steps of tissue regeneration; however, chronic or excessive inflammation can lead to permanent damage and pathological changes. In PHT, inflammation contributes on the one hand to liver fibrosis and on the other hand triggers splanchnic angiogenesis, which enforces the hyperdynamic circulation and thus worsens PHT. Since inflammatory markers strongly correlate with HVPG [56,57], modulating inflammation and associated pathways is a highly investigated rationale for treatment of PHT.

Thalidomide is a first-generation immunomodulatory drug, which inhibits the TNFα/NF-κB pathway and thus acts anti-inflammatory. In cirrhotic models, it improved intestinal mucosal damage, suppressed splanchnic angiogenesis and improved hepatic microvasculature, which translated into a decreased intrahepatic resistance and portal pressure [58–60]. Similar effects were seen in pre-hepatic PHT, induced by partial portal vein ligation (PPVL), where thalidomide treatment decreased NO production, the hyperdynamic circulation and PHT [61,62]. In a small pilot study, two weeks of thalidomide significantly decreased HVPG, where five out of six patients had a HVPG change greater 20% without altering systemic haemodynamics [63]. Of note, lenalidomide, a derivate of thalidomide, also exhibited anti-portal hypertensive effects in PPVL rats (*published as an abstract*) [64].

Further downstream inflammation and apoptosis are regulated by caspases. In a similar approach, the caspase inhibitor emricasan has been shown to reduce inflammation and fibrosis in cirrhotic rodent models [65,66] and transaminases in patients [67]. A multicentre phase 2 trial followed, showing significant decreases in HVPG after four weeks of therapy in first results presented as an abstract [68]. Another trial in patients with non-alcoholic steatohepatitis (NASH) and PHT has just been started [69].

Chronic inflammation is nurtured by reactive oxygen species (ROS), which can be targeted by antioxidative therapies [70]. Indeed, strategies for inhibiting ROS-producing enzymes (NAD(P)H oxidase by apocynin or haemooxygenase by tin porphyrins) significantly decreased splanchnic neovascularization and portal pressure in models of pre-hepatic and intrahepatic PHT [71–73], although the role of NAD(P)H oxidase has been questioned [74] and inhibition of haemooxygenase may also increase intrahepatic vascular resistance in cirrhosis [75]. Alternative approaches aimed to enforce ROS elimination via the manganese-dependent superoxide dismutase (MnSOD). Therefore, recombinant MnSOD or adenovector MnSOD gene transfer were successfully used in CCl4 rats to decrease ROS content and thus ameliorate liver cirrhosis and portal pressure [76,77]. In line, tempol, a small molecule and MnSOD mimetic, led to similar results with increased NO availability in sinusoidal endothelial cells and decreased portal pressure in CCl4 rats [78]. Moreover, scavengers of free radicals have been investigated. In an experimental study with CCl4 rats, cerium oxide nanoparticles displayed strong antioxidative effects and significantly reduced PHT [79] and, in a small RCT, vitamin C infusion improved intrahepatic endothelial dysfunction and prevented the postprandial HVPG increase [80].

Eicosanoids promote inflammation and vasoconstriction, and thus contribute to PHT. In liver cirrhosis, cyclooxygenase (COX)-derived prostanoids decrease NO bioavailability, cause endothelial dysfunction and increase the hepatic vascular tone [81–83]. Consequentially, chronic COX inhibition with (nitro)-flurbiprofen, celecoxib or thromboxan receptor blockade by terutroban decreased portal pressure in cirrhotic rats, which was accompanied by decreased liver fibrosis and angiogenesis [84–86]. Another pathway of metabolizing arachidonic acid, is via epoxygenases. Specific inhibition using MS-PPOH also significantly reduced portal pressure and increased response to acetylcholine in cirrhotic animals [87]. Although COX inhibitors are widely distributed in clinics, no human data of their effect on HVPG have been published yet. However, one RCT seems to be planned using the thromboxane receptor antagonist ifetroban [88].

In addition to the physicochemical damage, also bacteria may contribute to intestinal/hepatic inflammation and thus perpetuate PHT [89]. In cirrhotic patients, dysbiosis and bacterial overgrowth are commonly observed, increasing bacterial load and pathogenicity. Furthermore, PHT damages the intestinal barrier and thus increases translocation into the portal system [90]. Notably, NSBB therapy decreases intestinal permeability and inflammatory serum levels in CCl4 rats as well as in patients with cirrhosis [91,92], but also vice versa influencing the intestinal flora has shown to affect portal pressure. In germ-free mice, portal pressure rose significantly less after PPVL compared to wild-type mice [93]. Hence, the effects of antibiotic therapy on HVPG were intensively investigated in human trials. Rifaximin is entero-selective and approved for treatment of hepatic encephalopathy. In cirrhotic patients, a month of Rifaximin treatment decreased HVPG [94] and improved systemic haemodynamics [95], which furthermore reduced the risk of developing complications of PHT and improved survival [96]. Yet, a RCT (*published as an abstract*) could not confirm the beneficial effects of Rifaximin on haemodynamics in decompensated patients [97]. A prospective double-blind study investigating Rifaximin and propranolol combination therapy versus propranolol monotherapy is currently ongoing [98]. In contrast, treatment with norfloxacin had no effect on HVPG [99–101]. Another approach is to restore intestinal bacterial diversity by supplementing probiotics. While the impact of the probiotic VSL#3 alone on HVPG led to conflicting studies [102,103], a RCT observed an increase in haemodynamic response to NSBB in patients receiving adjunctive probiotics [104].

Anticoagulants

Cirrhotic patients suffer from a imbalance of anti- and procoagulatory factors, increasing the risk for bleedings, but also for thrombosis (especially in the portal venous system). While macro-thrombotic events (e.g. portal venous thrombosis) can be radiologically diagnosed, microthrombosis in the liver parenchyma (which were histologically characterized) cause localized hypoxia and infarctions [105]. Microthrombosis is closely linked to inflammation [106] and might contribute to an increase in intrahepatic vascular resistance and PHT. Indeed, anticoagulants have been shown to prevent hepatic fibrosis in cirrhotic models [107,108]. Furthermore, enoxaparin treatment prevented decompensation and improved survival in cirrhotic patients [109]. Yet, data on portal hypertensive effects are scarce.

Recently, Cerini *et al.* [110] found reductions in liver fibrosis and hepatic stellate cell activation in enoxaparin treated CCl4 cirrhotic rats, which translated into a significant decrease in portal pressure. However, a contrary abstract could not reproduce the beneficial effects of enoxaparin on liver fibrosis and PHT [111].

At the International Liver Congress 2016, rivaroxaban, a direct factor Xa inhibitor, has been presented to significantly decrease portal pressure in two different cirrhotic rat models and reduced the frequency of intrahepatic microthrombosis [112]. Of note, the use of direct-acting oral anticoagulants in cirrhotic patients seems to be effective and safe [113]. Hence, results of the ongoing CIRROXABAN study investigating survival, complications and effects on HVPG (as a secondary-outcome parameter) in cirrhotic patients with PHT receiving rivaroxaban are awaited to add more evidence for or against the use of anticoagulants in PHT [114].

Angiogenesis

Angiogenesis is triggered by hypoxia, inflammation and elevated vascular pressure. These conditions are present during hepatic fibrogenesis [115,116] and formation of porto-systemic collaterals [117], which are major drivers for the development of PHT. Thus, angiogenesis contributes to an increase in portal pressure. Vascular growth and remodelling are orchestrated by a plethora of cytokines, like vascular endothelial growth factor (VEGF), placental growth factor (PlGF) or platelet-derived growth factor (PDGF).

Blocking VEGF receptor 2 (with a monoclonal VEGFR2 antibody or semaxanib) indeed decreased hyperdynamic splanchnic circulation and porto-systemic collateral vessel formation in portal hypertensive rodents, but did not ameliorate portal pressure [117,118]. PlGF plays a crucial role especially during pathological angiogenesis and during vascular maturing. Hence, PlGF antibodies or PlGF knock-out decreased superior mesenteric blood flow and additionally decreased portal pressure in non-cirrhotic and in cirrhotic portal hypertensive animals [119,120]. Similarly, blockade of the PDGF receptor, which affects pericytes and activates HSCs, using a dominant-negative PDGF receptor encoding adenovirus decreased portal pressure and hepatic collagen content in cirrhotic rats [121].

The idea of combining growth hormone inhibition (with rapamycin+imatinib against VEGF/PDGF signalling) led to superior results [122]. Hence, oral tyrosin kinase inhibitors (Sorafenib [123–125], sunitinib [126], brivanib [127, 128] and regorafenib [129]), which have the ability to affect multiple branches of angiogenic pathways simultaneously, were successfully tested in cirrhotic and in non-cirrhotic PHT rats, uniformly describing a significant decrease in portal pressure and systemic shunting. Moreover, these tyrosin kinase inhibitors showed strong evidence to ameliorate liver fibrosis [130]. Of note, in cirrhotic rats, the beneficial effects of angiogenic blockade by Sorafenib synergistically added up to propranolol therapy [131].

So far, the potential of Sorafenib has been confirmed in two small human studies where significant anti-portal hypertensive effects have been described [132,133]. However, a small ($n = 9$) RCT addressing this question has shown no significant differences regarding HVPG decrease (*published as an abstract*) [134].

An additional rationale to modulate angiogenesis in PHT is to augment endogenous inhibitors of angiogenesis. Over-expression by adenovirus-mediated gene transfer of pigment epithelium-derived factor (PEDF) or vasohibin-1 also resulted in decreased mesenteric angiogenesis, porto-systemic shunting, PHT and liver fibrosis [135,136]. However, no human studies are currently available following this approach.

Although the above-mentioned studies are promising, a total blockade of angiogenic pathways might be deleterious, since angiogenesis is also required for hepatic tissue repair and fibrosis resolution [137]. Hence, the optimal window of opportunity for antiangiogenic therapies presumably is during PHT and porto-systemic collateral development, respectively.

Statins

Statins, initially designed as lipid-lowering drugs via inhibition of hydroxymethylglutaryl-CoA (HMG-CoA) reductase, have been shown to confer striking and potentially far more interesting vasoprotective effects. While statins are a cornerstone in cardiovascular prevention therapy [138], their use in the context of liver disease has been somewhat distrusted because of potential drug-induced liver injury [139]. However, over the years, the scepticism towards this drug class in chronic liver disease and in particular cirrhosis has turned into reserved positivism.

The first proof-of-concept study for statins dates from more than 10 years ago and notably was a clinical study. Zafra *et al.* showed in a small cohort of cirrhotic patients that short-term treatment with simvastatin increased hepatic NO and decreased hepatic resistance [140]. Further, simvastatin pretreatment significantly attenuated the postprandial increase in HVPG.

The modes of action of how statins increase NO bioavailability and decrease portal pressure are pleiotropic (well described by Noma *et al.* [141]) and have been dissected in several preclinical mechanistic studies. On the one hand, simvastatin treatment improved liver sinusoidal endothelial dysfunction by increasing Akt-dependent endothelial NOS (eNOS) phosphorylation (activity) and eNOS gene expression [142,143]. On the other hand, atorvastatin significantly decreased Rho-kinase activity and the association between RhoA and Ras [143], which regulate the vascular tone by inactivation of the myosin light-chain phosphatase and so maintain hepatic stellate cell contraction. The importance of RhoA and RhoA kinase for intrahepatic resistance in cirrhotic rats has been demonstrated independently by use of its inhibitor Y-27632, which significantly reduced portal pressure in cirrhotic rats [144,145].

In addition, statins (fluvastatin and atorvastatin) have been shown to ameliorate experimental liver injury, particularly in the early phase of liver fibrogenesis [146,147], and inhibit the activation of HSCs to myofibroblasts [148]. Hereby, the protective transcription factor Kruppel-like factor 2 (KLF2) plays a central role which is up-regulated by statins, especially under shear-stress conditions. *In vitro*, KLF2 strongly blocks HSC proliferation and expression of profibrotic and proangiogenic proteins [149,150]. In a confirmatory *in vivo* study, adenoviral transfection enhancing KLF2 expression changed HSC into a quiescent state. This reduced liver fibrosis and decreased portal pressure in CCl4 rats, which was accompanied by decreased hepatic vascular resistance and significant improvements in hepatic endothelial dysfunction [151].

While statins have been shown to be beneficial in cirrhotic PHT, the picture is to the contrary in pre-hepatic PHT. In PPVL models, statins aggravated angiogenesis and decreased porto-systemic collateral resistance, which could increase shunting or even portal pressure [152–154].

Encouraged by preclinical and preliminary clinical data, the first phase II RCT in 2009 fuelled the interest in statins for cirrhotic PHT, as it demonstrated that simvastatin was safe and

promoted a moderate decrease in portal pressure, when given both alone or on top of NSBB [155]. Interestingly, patients randomized to simvastatin showed an improvement in hepatic function, suggesting an additional amelioration of metabolic exchange at the liver microcirculation. A second three-month RCT confirmed that simvastatin lowers portal pressure and tends to improve liver function in cirrhotic patients [156]. Thereafter, a larger double-blind multicentre RCT was performed in the context of secondary prophylaxis of variceal bleeding as an add-on to standard medical and endoscopic treatment [157]. The results of this recently published study show that simvastatin administration did not improve the risk of re-bleeding, but was associated with a survival benefit in patients with Child-Pugh A/B cirrhosis. In another recent RCT (*published as an abstract*), patients treated with NSBB for primary prophylaxis and receiving additional simvastatin had a significantly stronger HVPG response [158], thus confirming previous studies.

Finally, two large retrospective cohort studies observed over 40% risk reduction for cirrhosis development, hepatocellular carcinoma (HCC) incidence, hepatic decompensation and death in hepatitis C-positive patients taking statins compared to those without [159,160].

Most recently, a nitric oxide-releasing atorvastatin (NCX 6560) has been studied in two experimental models of liver cirrhosis. While the beneficial effects of statins on liver profile and PHT could be confirmed, the parallel release of NO additionally improved intrahepatic endothelial dysfunction and reduced muscular and hepatic toxicity [161].

Farnesoid X receptor

A promising future target in chronic liver disease is the farnesoid X receptor (FXR). This bile-acid-responsive transcription factor belongs to the nuclear receptor superfamily and is highly expressed in the liver and the small intestine [162]. FXR controls the expression of genes involved in metabolic regulation, inflammation, hepatic fibrosis and vascular homeostasis [163,164].

The development of the semi-synthetic FXR agonist 6-ethyl-chenodeoxycholic acid, also known as obeticholic acid (OCA), opened the door for translational and clinical FXR research [165]. Meanwhile, non-steroidal FXR agonists (PX20606), which, in contrast to their steroidal counterparts, evade enterohepatic recirculation, are also increasingly being investigated [166,167].

From the perspective of PHT, FXR agonism seems a strategy worthy of pursuing due to strong preclinical evidence. In vascular endothelial cells, FXR activation increased eNOS and thus NO content [168], while, in endothelial cells and liver tissue, FXR suppressed the inflammatory response by reducing inducible NOS (iNOS) and COX2 expression [169,170]. In addition, FXR agonism improved liver injury in experimental cholestatic [171,172], toxic [173] and NASH liver disease models [174].

The first proof-of-concept study by Verbeke *et al.* demonstrated in two different cirrhotic rodent models that treatment with OCA improved PHT by decreasing the intrahepatic vascular tone without deleterious impact on mean arterial pressure or liver biochemistry [175]. Further evidence came by two subsequent rodent studies confirming the anti-portal hypertensive effects of FXR agonism with OCA and PX-20606, respectively [176,177]. The underlying molecular mechanisms involved affect (i) NO metabolism, (ii) H_2S production, (iii) hepatic inflammation and (iv) bacterial translocation:

- Asymmetric dimethylarginine is a circulating eNOS inhibitor [178] which correlates with HVPG [179] and which is degraded by dimethylarginine dimethylaminohydrolases (DDAH). In portal hypertensive rats, DDAH isoforms have been shown to be up-regulated by FXR agonists, thus restoring endothelial dysfunction and contributing to the decrease in portal pressure [175–177]. In addition, also eNOS expression and activity were stimulated upon FXR agonism [177].
- In CCl4 rats, FXR agonists protected against the down-regulation of cystathionase expression and increased the production of vasodilatory H_2S, which contributed to the decrease in portal pressure [177,180].
- Furthermore, in cirrhotic rats, FXR agonists significantly reduced liver inflammation and fibrosis, which was related to reduced expression of inflammatory and angiogenic cytokines [177,181]. *In vitro*, FXR prevented liver sinusoidal endothelial (LSECs) and Kupffer cell activation, while the role of HSCs remains to be elucidated, since some studies measured only insignificant expression levels of FXR in HSCs [182] or reported no effects upon FXR stimulation [181], while others report that FXR protects from ET1-mediated HSC contraction and thus decreases portal pressure [183,184].
- The beneficial effects of FXR in cirrhosis and PHT are also mediated via its enteroprotective properties. FXR agonists have been shown to reduce bacterial overgrowth, intestinal inflammation and mucosal injury, which improved the gut barrier and reduced bacterial translocation [185–187]. Accordingly, also clinical observations found that cirrhotic patients with certain FXR polymorphisms predispose to develop spontaneous bacterial peritonitis [188].

In a recent abstract, the haemodynamic effects of a new FXR agonist (GS-9674) in combination with NSBB therapy were explored in cirrhotic NASH animals. Indeed, after long-term therapy, dose-dependent antifibrotic effects and amelioration of PHT were confirmed. The combination with propranolol was safe and resulted in an additional decrease in mesenteric hyperperfusion [189].

Going from bench to bedside, at present, there is only one trial assessing the impact of FXR agonism in patients with cirrhotic PHT. In this open label phase 2 proof-of-concept study, Mookerjee *et al.* reported that, after a week of OCA, nine out of 16 patients with alcoholic cirrhosis responded with a mean HVPG reduction of 28% (published as an abstract) [190]. Final results are still awaited, as are larger controlled confirmatory trials. In respect of antifibrotic properties, the FLINT trial confirmed amelioration of liver fibrosis in NASH patients treated with OCA [191]. Taken together, FXR agonism has shown the positive first steps and further confirmatory data are eagerly awaited.

Renin–angiotensin–aldosterone system

The renin–angiotensin–aldosterone (RAA) system was acknowledged already 35 years ago in portal and systemic haemodynamics [192]. As such, plasma renin concentration represents an independent risk factor for mortality and is associated with liver dysfunction in patients with cirrhosis [193]. Thus, angiotensin-converting-enzyme inhibitors (ACEi, e.g. captopril), angiotensin receptor blockers (ARB, e.g. losartan, candesartan and irbesartan) and aldosteron antagonists (e.g. spironolactone) have been tested in numerous rodent and human trials to reduce RAA-mediated signalling. In an elegant meta-analysis by Tandon *et al.*, including 19 controlled trials with a total of >650

patients, efficacy of these drugs has been critically scrutinized [194]. In patients with Child A cirrhosis, the HVPG reduction with ACEi or ARB was described to be similar to that of NSBBs (–17% *vs* –21% mean HVPG decrease). However, decompensated patients (Child B/C) had an elevated risk of hypotension, worsening of hyperdynamic circulation or renal insufficiency. Disenchantingly, the add-on approach of using spironolactone [195], irbesartan [196] or candesartan [197] to NSBB therapy resulted in no additional HVPG decrease, and spironolactone in addition to NSBB did not help in preventing first variceal bleeding [198].

The findings that angiotensin II affects HSCs (leading to contraction and increased collagen expression) [199,200] and cholangiocytes (stimulating biliary proliferation) [201] relaunched the interest in the RAA system from an antifibrotic perspective. Further experimental studies confirmed that angiotensin II exacerbates liver fibrosis [202] while losartan or spironolactone reduced collagen deposition, accumulation of myofibroblasts and inflammation [203,204]—thus improving PHT [204]. These beneficial antifibrotic effects were confirmed in small trials in patients with advanced fibrosis or early cirrhosis of different etiologies [205–208], but are offset by others, as in the HALT-C cohort, where ACEi/ARB therapy did not decelerate the progression of hepatic fibrosis [209].

Given the potential of the RAA system (especially in compensated cirrhotic patients) and the limitation of currently available drugs, alternatives to ACEi or ARBs are the focus of research.

Following the downstream pathway of the angiotensin receptor, Janus kinase [210] and subsequently Rho-kinase [204] have been identified as key mediators of (anti-) portal hypertensive effects. Indeed, the Janus kinase inhibitor AG490 significantly attenuated liver fibrosis *in vivo* and *in vitro* and decreased hepatic vascular resistance and portal pressure in cirrhotic rats [210–212]. In contrast to ACEi/ARB, add-on therapy with AG490 to propranolol resulted in an additive portal pressure-lowering effect in cirrhotic animals [213]. Similarly, the Rho-kinase inhibitor Y-27632 decreased fibrosis and lowered portal pressure without major systemic side effects [144,145] in animal studies. However, due to the lack of cellular specificity, no human studies have been performed yet.

An additional approach is to augment liver-selectivity by coupling drugs to a hepato-specific carrier. Indeed, HSC-selective 'mannose-6-phosphate modified human serum albumin' significantly improved effectiveness of losartan [203] or the Rho-kinase inhibitor Y26732 [145] in experimental studies and thus supported the decrease in portal pressure.

Next to the classic RAA system, ACE2, its product angiotensin 1–7 and its receptor Mas represent an alternative/balancing downstream pathway, which partly opposes the angiotensin receptor [214]. This vasoactive pathway is up-regulated in the splanchnic aeria but also in livers of patients and rats with cirrhosis [215–217]. Indeed, the Mas receptor agonists (e.g. AVE0991) inhibited intrahepatic vasoconstriction, reduced liver fibrosis and decreased portal pressure in experimental cirrhosis [216,218,219]. However, stimulation with angiotensin 1–7 exacerbates splanchnic vasodilation in cirrhotic animals and likely increases porto-systemic shunting [217]. Yet, also the absolute contrary—namely blocking Mas with A779—led to a net decrease in portal pressure in cirrhotic animals [217], leaving a lot of room for optimizing this therapeutic approach before translating it into clinics.

Aside from the RAA system, also vasopressin contributes to the tight regulation of water/electrolyte homeostasis and diuresis by retaining water. According to a large meta-analysis, in cirrhotic patients, antagonizing vasopressin using vaptans might have a small benefit on hyponatremia and ascites, but does not affect mortality [220]. A recent RCT concluded that conivaptan was generally found to be safe and well tolerated in cirrhotic patients with clinically significant PHT but acute infusion did not change HVPG [221]. Thus, drugs were refined and, in an experimental trial, using the partial vasopressin agonists FE 204038, cirrhotic rats presented a dose-dependent decrease in portal pressure and an increase in systemic vascular resistance without changes in mean arterial pressure [222]. Based on these data, a RCT with the partial vasopressin receptor agonist FE 204205 in patients with cirrhotic portal hypertension has been initiated—which is currently still ongoing [223].

Metabolism and foods

The liver plays a central role in energy metabolism, which is deteriorated by liver cirrhosis. Thus, about 30% of patients with cirrhosis suffer from diabetes mellitus [224]. Furthermore, sarcopenia is common and special diets are recommended [225]. As already described for statins, also other drugs affecting the metabolism and even foods have been studied and some presented remarkable effects on portal pressure.

Metformin, which is used for type 2 diabetes, caused significant reductions in liver fibrosis, inflammation and portal pressure in CCl4 cirrhotic rats. Notably, this effect was additive to NSBB treatment [226]. Similarly, liraglutide, a glucagone-like peptide receptor agonist, reduced HSC proliferation and portal pressure in cirrhotic rats and additionally showed antifibrotic effects in human liver tissue (*published as an abstract*) [227]. Also, the antidiabetic pioglitazone, which stimulates the nuclear peroxisome proliferator-activated receptor (PPAR) gamma, decreased porto-systemic shunting by modulating inflammation and angiogenesis in cirrhotic and non-cirrhotic portal hypertensive rats, yet it had no impact on portal pressure [228]. On the contrary, this was achieved by the PPAR-alpha agonist fenofibrat (a drug against hyperlipidemia), which decreased portal pressure in cirrhotic rats by a reduced thromboxan production and increased NO bioavailability. In this study, fenofibrat treatment also significantly reduced hepatic fibrosis and increased mean arterial pressure [229]. While the metabolic syndrome with hyperglycemia and hyperlipidemia likely contributes to liver fibrosis, and is an established risk factor for NASH, it is interesting to see that also a week of leptin receptor blockade slightly decrease portal pressure in a CCl4 model [230]. Another orexogenic receptor is the endocannabinoid receptor, of which type 2 seems to play a role in hepatic fibrogenesis and PHT. Notably, receptor-deficient mice suffered from intensified steatosis and fibrogenesis [231], while agonists (JWH-015, JWH-133, GP 1a, AM1241) reduced hepatic fibrosis and portal pressure by inhibiting inflammation and angiogenesis [232–234]. Of note, long-term cannabinoid therapy also decreases bacterial translocation in cirrhotic rats with ascites [235].

Since it is known that coffee is hepatoprotective, it is interesting to know that caffeine has also been shown to decrease portal pressure, ameliorate hyperdynamic circulation, porto-systemic shunting, mesenteric angiogenesis, hepatic angiogenesis and fibrosis in cirrhotic rats [236]. Also, flavonoid-rich (dark) chocolate, which has antioxidative properties, successfully improved HVPG in a small RCT [237]. The antioxidative agent resveratrol has its highest concentrations in berries, yet artificially high amounts were necessary to show its beneficial effects in CCl4 rats, where it improved endothelial dysfunction, decreased hepatic fibrosis and portal pressure [238]. The amino

acid taurine (which occurs in energy drinks) physiologically builds bile-acid conjugates and acts as an antioxidative. Beneficial effects on portal pressure were seen in a cirrhotic rat study [239] and in a small RCT where HVPG decreased significantly after long-term high-dose taurin administration (*published as an abstract*) [240].

Even though these drugs might be used when clinically indicated and thus give an additional benefit to PHT therapy, more data are necessary to draw detailed conclusions or give clear recommendations.

Summary and outlook

In the last 20 years, many studies have been conducted with the aim of finding new anti-portal hypertensive drugs. While knowledge has broadened immensely, only a few molecules made it into human trials. Yet, this continuous evolving research let us speculate that, sooner or later, the armamentarium for the treatment of PHT undoubtedly will extend. The currently available drugs for PHT (NSBBs) target the dynamic component. Hence, add-on therapy combinations or drugs which act antifibrotic and decrease PHT might have the highest chance of success in clinics. Indeed, treatment of the underlying disease is a significant contributor to therapy of PHT. However, since the static component (fibrosis) changes much slower, drugs affecting fibrogenesis, fibrosis and fibrosis resolution have to be distinguished and investigated differentially.

For future experimental trials, it is recommended to assess candidates not only in one particular setting, but in multiple models, and to consider the different stages of PHT/fibrosis development. Thinking back from bed to benchside, it is necessary to find a drug that safely can be taken for a long time without losing its effectiveness and with a low risk for drug–drug interactions.

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References

1. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;**63**:743–52.
2. Reiberger T, Mandorfer M. Beta adrenergic blockade and decompensated cirrhosis. *J Hepatol* 2017;**66**:849–59.
3. Mandorfer M, Reiberger T. Beta blockers and cirrhosis, 2016. *Dig Liver Dis* 2017;**49**:3–10.
4. Reiberger T, Payer BA, Schwabl P *et al*. Nebivolol treatment increases splanchnic blood flow and portal pressure in cirrhotic rats via modulation of nitric oxide signalling. *Liver Int* 2013;**33**:561–8.
5. Hemstreet BA. Evaluation of carvedilol for the treatment of portal hypertension. *Pharmacotherapy* 2004;**24**:94–104.
6. Banares R, Moitinho E, Piqueras B *et al*. Carvedilol, a new nonselective beta-blocker with intrinsic anti-Alpha1-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. *Hepatology* 1999;**30**:79–83.
7. Reiberger T, Ulbrich G, Ferlitsch A *et al*. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. *Gut* 2013;**62**:1634–41.
8. Albillos A, Garcia-Pagan JC, Iborra J *et al*. Propranolol plus prazosin compared with propranolol plus isosorbide-5-mononitrate in the treatment of portal hypertension. *Gastroenterology* 1998;**115**:116–23.
9. Villanueva C, Aracil C, Colomo A *et al*. Clinical trial: a randomized controlled study on prevention of variceal rebleeding comparing nadolol + ligation vs. hepatic venous pressure gradient-guided pharmacological therapy. *Aliment Pharmacol Ther* 2009;**29**:397–408.
10. Albillos A, Banares R, Gonzalez M *et al*. Value of the hepatic venous pressure gradient to monitor drug therapy for portal hypertension: a meta-analysis. *Am J Gastroenterol* 2007;**102**:1116–26.
11. Mandorfer M, Bota S, Schwabl P *et al*. Nonselective beta blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. *Gastroenterology* 2014;**146**:1680–90. e1.
12. Shah N, Montes de Oca M, Shah N *et al*. Treatment with an alpha 2a adrenoreceptor antagonist modulates hepatic inflammation, markedly reduces portal pressure, and improves arterial pressure and hepatic blood flow in cirrhotic rats. *Gut* 2010;**59**:A25.
13. Jones H, Sharma V, Brandao da Silva A *et al*. Noradrenaline potentiates portal hypertension through the alpha 2a adrenergic receptor—a target for therapy in portal hypertension. *J Hepatol* 2016;**64**:S446.
14. Trebicka J, Hennenberg M, Schulze Probsting A *et al*. Role of beta3-adrenoceptors for intrahepatic resistance and portal hypertension in liver cirrhosis. *Hepatology* 2009;**50**:1924–35.
15. Vasina V, Giannone F, Domenicali M *et al*. Portal hypertension and liver cirrhosis in rats: effect of the beta3-adrenoceptor agonist SR58611A. *Br J Pharmacol* 2012;**167**:1137–47.
16. Hartl J, Dietrich P, Moleda L *et al*. Neuropeptide Y restores non-receptor-mediated vasoconstrictive action in superior mesenteric arteries in portal hypertension. *Liver Int* 2015;**35**:2556–63.
17. Wiest R, Jurzik L, Moleda L *et al*. Enhanced Y1-receptor-mediated vasoconstrictive action of neuropeptide Y (NPY) in superior mesenteric arteries in portal hypertension. *J Hepatol* 2006;**44**:512–19.
18. Moleda L, Trebicka J, Dietrich P *et al*. Amelioration of portal hypertension and the hyperdynamic circulatory syndrome in cirrhotic rats by neuropeptide Y via pronounced splanchnic vasoaction. *Gut* 2011;**60**:1122–32.
19. Reboredo M, Chang HC, Barbero R *et al*. Zolmitriptan: a novel portal hypotensive agent which synergizes with propranolol in lowering portal pressure. *PloS One* 2013;**8**:e52683.
20. Wiest R, Groszmann RJ. The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough. *Hepatology* 2002;**35**:478–91.
21. Navasa M, Chesta J, Bosch J *et al*. Reduction of portal pressure by isosorbide-5-mononitrate in patients with cirrhosis: effects on splanchnic and systemic hemodynamics and liver function. *Gastroenterology* 1989;**96**:1110–18.
22. Garcia-Pagan JC, Morillas R, Banares R *et al*. Propranolol plus placebo versus propranolol plus isosorbide-5-mononitrate in the prevention of a first variceal bleed: a double-blind RCT. *Hepatology* 2003;**37**:1260–6.
23. Fiorucci S, Antonelli E, Brancaleone V *et al*. NCX-1000, a nitric oxide-releasing derivative of ursodeoxycholic acid, ameliorates portal hypertension and lowers norepinephrine-induced intrahepatic resistance in the isolated and perfused rat liver. *J Hepatol* 2003;**39**:932–9.
24. Berzigotti A, Bellot P, De Gottardi A *et al*. NCX-1000, a nitric oxide-releasing derivative of UDCA, does not decrease portal

pressure in patients with cirrhosis: results of a randomized, double-blind, dose-escalating study. *Am J Gastroenterol* 2010;**105**:1094–1101.
25. Duong HT, Dong Z, Su L *et al*. The use of nanoparticles to deliver nitric oxide to hepatic stellate cells for treating liver fibrosis and portal hypertension. *Small* 2015;**11**:2291–2304.
26. Biecker E, Trebicka J, Kang A *et al*. Treatment of bile duct-ligated rats with the nitric oxide synthase transcription enhancer AVE 9488 ameliorates portal hypertension. *Liver Int* 2008;**28**:331–8.
27. Matei V, Rodriguez-Vilarrupla A, Deulofeu R *et al*. Three-day tetrahydrobiopterin therapy increases in vivo hepatic NOS activity and reduces portal pressure in CCl4 cirrhotic rats. *J Hepatol* 2008;**49**:192–7.
28. Matei V, Rodriguez-Vilarrupla A, Deulofeu R *et al*. The eNOS cofactor tetrahydrobiopterin improves endothelial dysfunction in livers of rats with CCl4 cirrhosis. *Hepatology* 2006;**44**:44–52.
29. Reverter E, Mesonero F, Seijo S *et al*. Effects of sapropterin on portal and systemic hemodynamics in patients with cirrhosis and portal hypertension: a bicentric double-blind placebo-controlled study. *Am J Gastroenterol* 2015;**110**:985–92.
30. Halverscheid L, Deibert P, Schmidt R *et al*. Phosphodiesterase-5 inhibitors have distinct effects on the hemodynamics of the liver. *BMC Gastroenterol* 2009;**9**:69.
31. Colle I, De Vriese AS, Van Vlierberghe H *et al*. Systemic and splanchnic haemodynamic effects of sildenafil in an in vivo animal model of cirrhosis support for a risk in cirrhotic patients. *Liver Int* 2004;**24**:63–8.
32. Lee KC, Yang YY, Huang YT *et al*. Administration of a low dose of sildenafil for 1 week decreases intrahepatic resistance in rats with biliary cirrhosis: the role of NO bioavailability. *Clin Sci (Lond)* 2010;**119**:45–55.
33. Choi SM, Shin JH, Kim JM *et al*. Effect of udenafil on portal venous pressure and hepatic fibrosis in rats: a novel therapeutic option for portal hypertension. *Arzneimittelforschung* 2009;**59**:641–6.
34. Lee KC, Yang YY, Wang YW *et al*. Acute administration of sildenafil enhances hepatic cyclic guanosine monophosphate production and reduces hepatic sinusoid resistance in cirrhotic patients. *Hepatol Res* 2008;**38**:1186–93.
35. Clemmesen JO, Giraldi A, Ott P *et al*. Sildenafil does not influence hepatic venous pressure gradient in patients with cirrhosis. *World J Gastroenterol* 2008;**14**:6208–12.
36. Tandon P, Inayat I, Tal M *et al*. Sildenafil has no effect on portal pressure but lowers arterial pressure in patients with compensated cirrhosis. *Clin Gastroenterol Hepatol* 2010;**8**:546–9.
37. Kreisel W, Deibert P, Kupcinskas L *et al*. The phosphodiesterase-5-inhibitor udenafil lowers portal pressure in compensated preascitic liver cirrhosis. A dose-finding phase-II-study. *Dig Liver Dis* 2015;**47**:144–50.
38. Deibert P, Schumacher YO, Ruecker G *et al*. Effect of vardenafil, an inhibitor of phosphodiesterase-5, on portal haemodynamics in normal and cirrhotic liver: results of a pilot study. *Aliment Pharmacol Ther* 2006;**23**:121–8.
39. https://clinicaltrials.gov/ct2/show/NCT02344823.
40. Knorr A, Hirth-Dietrich C, Alonso-Alija C *et al*. Nitric oxide-independent activation of soluble guanylate cyclase by BAY 60–2770 in experimental liver fibrosis. *Arzneimittelforschung* 2008;**58**:71–80.
41. Xie G, Wang X, Wang L *et al*. Role of differentiation of liver sinusoidal endothelial cells in progression and regression of hepatic fibrosis in rats. *Gastroenterology* 2012;**142**:918–27.e6.
42. Schwabl P, Brusilowska K, Riedl F *et al*. The guanylyl cyclase stimulator riociguat reduces liver fibrosis and portal pressure in cirrhotic rats. *J Hepatol* 2016;**64**:S140.
43. Watanabe N, Takashimizu S, Nishizaki Y *et al*. An endothelin A receptor antagonist induces dilatation of sinusoidal endothelial fenestrae: implications for endothelin-1 in hepatic microcirculation. *J Gastroenterol* 2007;**42**:775–82.
44. Feng HQ, Weymouth ND, Rockey DC. Endothelin antagonism in portal hypertensive mice: implications for endothelin receptor-specific signaling in liver disease. *Am J Physiol Gastrointest Liver Physiol* 2009;**297**:G27–33.
45. Cavasin MA, Semus H, Pitts K *et al*. Acute effects of endothelin receptor antagonists on hepatic hemodynamics of cirrhotic and noncirrhotic rats. *Can J Physiol Pharmacol* 2010;**88**:636–43.
46. Hsu SJ, Lin TY, Wang SS *et al*. Endothelin receptor blockers reduce shunting and angiogenesis in cirrhotic rats. *Eur J Clin Invest* 2016;**46**:572–80.
47. Cho JJ, Hocher B, Herbst H *et al*. An oral endothelin-A receptor antagonist blocks collagen synthesis and deposition in advanced rat liver fibrosis. *Gastroenterology* 2000;**118**:1169–78.
48. Kojima H, Yamao J, Tsujimoto T *et al*. Mixed endothelin receptor antagonist, SB209670, decreases portal pressure in biliary cirrhotic rats in vivo by reducing portal venous system resistance. *J Hepatol* 2000;**32**:43–50.
49. Zipprich A, Schenkel E, Gittinger F *et al*. Selective endothelin-a blockade decreases portal pressure in patients with cirrhosis: a pilot study combining a local intraarterial and systemic administration. *J Hepatol* 2016;**64**:S247.
50. Lebrec D, Bosch J, Jalan R *et al*. Hemodynamics and pharmacokinetics of tezosentan, a dual endothelin receptor antagonist, in patients with cirrhosis. *Eur J Clin Pharmacol* 2012;**68**:533–41.
51. Tripathi D, Therapondos G, Ferguson JW *et al*. Endothelin-1 contributes to maintenance of systemic but not portal haemodynamics in patients with early cirrhosis: a randomised controlled trial. *Gut* 2006;**55**:1290–5.
52. http://www.clinicaltrialsregister.eu/ctr-search/trial/2014–004624–21/ES.
53. http://www.clinicaltrialsregister.eu/ctr-search/trial/2011–001139–22/AT.
54. Heller J, Schepke M, Neef M *et al*. Increased urotensin II plasma levels in patients with cirrhosis and portal hypertension. *J Hepatol* 2002;**37**:767–72.
55. Trebicka J, Leifeld L, Hennenberg M *et al*. Hemodynamic effects of urotensin II and its specific receptor antagonist palosuran in cirrhotic rats. *Hepatology* 2008;**47**:1264–76.
56. Mehta G, Gustot T, Mookerjee RP *et al*. Inflammation and portal hypertension—the undiscovered country. *J Hepatol* 2014;**61**:155–63.
57. Schwabl P, Mandorfer M, Steiner S *et al*. Interferon-free regimens improve portal hypertension and histological necroinflammation in HIV/HCV patients with advanced liver disease. *Aliment Pharmacol Ther* 2017;**45**:139–49.
58. Li TH, Huang CC, Yang YY *et al*. Thalidomide improves the intestinal mucosal injury and suppresses mesenteric angiogenesis and vasodilatation by down-regulating inflammasomes-related cascades in cirrhotic rats. *PloS One* 2016;**11**:e0147212.
59. Yang YY, Lee KC, Huang YT *et al*. Inhibition of hepatic tumour necrosis factor-alpha attenuates the anandamide-induced vasoconstrictive response in cirrhotic rat livers. *Liver Int* 2009;**29**:678–85.

60. Yang YY, Huang YT, Lin HC *et al*. Thalidomide decreases intrahepatic resistance in cirrhotic rats. *Biochem Biophys Res Commun* 2009;**380**:666–72.
61. Lopez-Talavera JC, Cadelina G, Olchowski J *et al*. Thalidomide inhibits tumor necrosis factor alpha, decreases nitric oxide synthesis, and ameliorates the hyperdynamic circulatory syndrome in portal-hypertensive rats. *Hepatology* 1996;**23**:1616–21.
62. Theodorakis NG, Wang YN, Korshunov VA *et al*. Thalidomide ameliorates portal hypertension via nitric oxide synthase independent reduced systolic blood pressure. *World J Gastroenterol* 2015;**21**:4126–35.
63. Austin AS, Mahida YR, Clarke D *et al*. A pilot study to investigate the use of oxpentifylline (pentoxifylline) and thalidomide in portal hypertension secondary to alcoholic cirrhosis. *Aliment Pharmacol Ther* 2004;**19**:79–88.
64. Payer B, Reiberger T, Schwabl P *et al*. Lenalidomide ameliorates the portal hypertensive syndrome in non-cirrhotic and cirrhotic portal hypertensive animals. *J Hepatol* 2013;**58**:S242.
65. Barreyro FJ, Holod S, Finocchietto PV *et al*. The pan-caspase inhibitor Emricasan (IDN-6556) decreases liver injury and fibrosis in a murine model of non-alcoholic steatohepatitis. *Liver Int* 2015;**35**:953–66.
66. Gracia-Sancho J, Contreras P, Vila S *et al*. The pan caspase inhibitor emricasan improves the hepatic microcirculatory dysfunction of CCl4-cirrhotic rats leading to portal hypertension amelioration and cirrhosis regression. *Hepatology* 2016;**64**:1043A.
67. Pockros PJ, Schiff ER, Shiffman ML *et al*. Oral IDN-6556, an antiapoptotic caspase inhibitor, may lower aminotransferase activity in patients with chronic hepatitis C. *Hepatology* 2007;**46**:324–9.
68. Garcia-Tsao G, Fuchs M, Shiffman M *et al*. Emricasan (IDN-6556) administered orally for 28 days lowers portal pressure in patients with compensated cirrhosis and severe portal hypertension. *Hepatology* 2015;**62**:1382A.
69. https://clinicaltrials.gov/ct2/show/NCT02230683.
70. Rodriguez-Vilarrupla A, Bosch J, Garcia-Pagan JC. Potential role of antioxidants in the treatment of portal hypertension. *J Hepatol* 2007;**46**:193–7.
71. Angermayr B, Fernandez M, Mejias M *et al*. NAD(P)H oxidase modulates angiogenesis and the development of portosystemic collaterals and splanchnic hyperaemia in portal hypertensive rats. *Gut* 2007;**56**:560–4.
72. Angermayr B, Mejias M, Gracia-Sancho J *et al*. Heme oxygenase attenuates oxidative stress and inflammation, and increases VEGF expression in portal hypertensive rats. *J Hepatol* 2006;**44**:1033–9.
73. Qin J, He Y, Duan M *et al*. Effects of Nuclear Factor-E2-related factor 2/Heme Oxygenase 1 on splanchnic hemodynamics in experimental cirrhosis with portal hypertension. *Microvasc Res* 2016;**111**:12–19.
74. Gracia-Sancho J, Lavina B, Rodriguez-Vilarrupla A *et al*. Evidence against a role for NADPH oxidase modulating hepatic vascular tone in cirrhosis. *Gastroenterology* 2007;**133**:959–66.
75. Van Landeghem L, Laleman W, Vander Elst I *et al*. Carbon monoxide produced by intrasinusoidally located haemoxygenase-1 regulates the vascular tone in cirrhotic rat liver. *Liver Int* 2009;**29**:650–60.
76. Guillaume M, Rodriguez-Vilarrupla A, Gracia-Sancho J *et al*. Recombinant human manganese superoxide dismutase reduces liver fibrosis and portal pressure in CCl4-cirrhotic rats. *J Hepatol* 2013;**58**:240–6.
77. Lavina B, Gracia-Sancho J, Rodriguez-Vilarrupla A *et al*. Superoxide dismutase gene transfer reduces portal pressure in CCl4 cirrhotic rats with portal hypertension. *Gut* 2009;**58**:118–25.
78. Garcia-Caldero H, Rodriguez-Vilarrupla A, Gracia-Sancho J *et al*. Tempol administration, a superoxide dismutase mimetic, reduces hepatic vascular resistance and portal pressure in cirrhotic rats. *J Hepatol* 2011;**54**:660–5.
79. Oro D, Yudina T, Fernandez-Varo G *et al*. Cerium oxide nanoparticles reduce steatosis, portal hypertension and display anti-inflammatory properties in rats with liver fibrosis. *J Hepatol* 2016;**64**:691–8.
80. Hernandez-Guerra M, Garcia-Pagan JC, Turnes J *et al*. Ascorbic acid improves the intrahepatic endothelial dysfunction of patients with cirrhosis and portal hypertension. *Hepatology* 2006;**43**:485–91.
81. Graupera M, Garcia-Pagan JC, Abraldes JG *et al*. Cyclooxygenase-derived products modulate the increased intrahepatic resistance of cirrhotic rat livers. *Hepatology* 2003;**37**:172–81.
82. Graupera M, March S, Engel P *et al*. Sinusoidal endothelial COX-1-derived prostanoids modulate the hepatic vascular tone of cirrhotic rat livers. *Am J Physiol Gastrointest Liver Physiol* 2005;**288**:G763–70.
83. Rosado E, Rodriguez-Vilarrupla A, Gracia-Sancho J *et al*. Interaction between NO and COX pathways modulating hepatic endothelial cells from control and cirrhotic rats. *J Cell Mol Med* 2012;**16**:2461–70.
84. Laleman W, Van Landeghem L, Van der Elst I *et al*. Nitroflurbiprofen, a nitric oxide-releasing cyclooxygenase inhibitor, improves cirrhotic portal hypertension in rats. *Gastroenterology* 2007;**132**:709–19.
85. Gao JH, Wen SL, Yang WJ *et al*. Celecoxib ameliorates portal hypertension of the cirrhotic rats through the dual inhibitory effects on the intrahepatic fibrosis and angiogenesis. *PloS One* 2013;**8**:e69309.
86. Rosado E, Rodriguez-Vilarrupla A, Gracia-Sancho J *et al*. Terutroban, a TP-receptor antagonist, reduces portal pressure in cirrhotic rats. *Hepatology* 2013;**58**:1424–35.
87. Di Pascoli M, Zampieri F, Verardo A *et al*. Inhibition of epoxyeicosatrienoic acid production in rats with cirrhosis has beneficial effects on portal hypertension by reducing splanchnic vasodilation. *Hepatology* 2016;**64**:923–30.
88. https://clinicaltrials.gov/ct2/show/NCT02802228.
89. Bellot P, Garcia-Pagan JC, Frances R *et al*. Bacterial DNA translocation is associated with systemic circulatory abnormalities and intrahepatic endothelial dysfunction in patients with cirrhosis. *Hepatology* 2010;**52**:2044–52.
90. Aguirre Valadez JM, Rivera-Espinosa L, Mendez-Guerrero O *et al*. Intestinal permeability in a patient with liver cirrhosis. *Ther Clin Risk Manag* 2016;**12**:1729–48.
91. Perez-Paramo M, Munoz J, Albillos A *et al*. Effect of propranolol on the factors promoting bacterial translocation in cirrhotic rats with ascites. *Hepatology* 2000;**31**:43–8.
92. Reiberger T, Ferlitsch A, Payer BA *et al*. Non-selective beta-blocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. *J Hepatol* 2013;**58**:911–21.
93. Moghadamrad S, McCoy KD, Geuking MB *et al*. Attenuated portal hypertension in germ-free mice: function of bacterial flora on the development of mesenteric lymphatic and blood vessels. *Hepatology* 2015;**61**:1685–95.
94. Vlachogiannakos J, Saveriadis AS, Viazis N *et al*. Intestinal decontamination improves liver haemodynamics in

patients with alcohol-related decompensated cirrhosis. *Aliment Pharmacol Ther* 2009;**29**:992–9.
95. Kalambokis GN, Mouzaki A, Rodi M *et al*. Rifaximin improves systemic hemodynamics and renal function in patients with alcohol-related cirrhosis and ascites. *Clin Gastroenterol Hepatol* 2012;**10**:815–18.
96. Vlachogiannakos J, Viazis N, Vasianopoulou P *et al*. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. *J Gastroenterol Hepatol* 2013;**28**:450–5.
97. Kimer N, Pedersen J, Busk T *et al*. Rifaximin has no effect on hemodynamics in decompensated cirrhosis: a randomized, double blind, placebo controlled trial. *Hepatology* 2016;**64**: 1041A.
98. https://clinicaltrials.gov/ct2/show/NCT01897051.
99. Hennenberg M, Trebicka J, Buecher D *et al*. Lack of effect of norfloxacin on hyperdynamic circulation in bile duct-ligated rats despite reduction of endothelial nitric oxide synthase function: result of unchanged vascular Rho-kinase? *Liver Int* 2009;**29**:933–41.
100. Rasaratnam B, Kaye D, Jennings G *et al*. The effect of selective intestinal decontamination on the hyperdynamic circulatory state in cirrhosis: *a randomized trial*. *Ann Intern Med* 2003;**139**:186–93.
101. Kemp W, Colman J, Thompson K *et al*. Norfloxacin treatment for clinically significant portal hypertension: results of a randomised double-blind placebo-controlled crossover trial. *Liver Int* 2009;**29**:427–33.
102. Jayakumar S, Carbonneau M, Hotte N *et al*. VSL#3 (R) probiotic therapy does not reduce portal pressures in patients with decompensated cirrhosis. *Liver Int* 2013;**33**:1470–7.
103. Rincon D, Vaquero J, Hernando A *et al*. Oral probiotic VSL#3 attenuates the circulatory disturbances of patients with cirrhosis and ascites. *Liver Int* 2014;**34**:1504–12.
104. Gupta N, Kumar A, Sharma P *et al*. Effects of the adjunctive probiotic VSL#3 on portal haemodynamics in patients with cirrhosis and large varices: a randomized trial. *Liver Int* 2013;**33**:1148–57.
105. Wanless IR, Wong F, Blendis LM *et al*. Hepatic and portal vein thrombosis in cirrhosis: possible role in development of parenchymal extinction and portal hypertension. *Hepatology* 1995;**21**:1238–47.
106. Koupenova M, Kehrel BE, Corkrey HA *et al*. Thrombosis and platelets: an update. *Eur Heart J* 2017;**38**:785–91.
107. Calvaruso V, Maimone S, Gatt A *et al*. Coagulation and fibrosis in chronic liver disease. *Gut* 2008;**57**:1722–7.
108. Jairath V, Burroughs AK. Anticoagulation in patients with liver cirrhosis: complication or therapeutic opportunity? *Gut* 2013;**62**:479–82.
109. Villa E, Cammà C, Marietta M *et al*. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology* 2012;**143**: 1253–60.e1-4.
110. Cerini F, Vilaseca M, Lafoz E *et al*. Enoxaparin reduces hepatic vascular resistance and portal pressure in cirrhotic rats. *J Hepatol* 2016;**64**:834–42.
111. Fortea J, Zipprich A, Mena C *et al*. Enoxaparin treatment does not ameliorate liver fibrosis or portal hypertension in experimental models of cirrhosis in rats. *Hepatology* 2015;**62**:951A.
112. Vilaseca M, Lopez-Sanjurjo C, Lafoz E *et al*. Rivaroxaban reduces portal hypertension in cirrhotic rats by deactivating hepatic stellate cells and reducing intrahepatic microthrombosis. *J Hepatol* 2016;**64**:S710.
113. De Gottardi A, Trebicka J, Klinger C *et al*. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. *Liver Int* 2016.
114. https://clinicaltrials.gov/ct2/show/NCT02643212.
115. Corpechot C, Barbu V, Wendum D *et al*. Hypoxia-induced VEGF and collagen I expressions are associated with angiogenesis and fibrogenesis in experimental cirrhosis. *Hepatology* 2002;**35**:1010–21.
116. Yoshiji H, Kuriyama S, Yoshii J *et al*. Vascular endothelial growth factor and receptor interaction is a prerequisite for murine hepatic fibrogenesis. *Gut* 2003;**52**:1347–54.
117. Fernandez M, Vizzutti F, Garcia-Pagan JC *et al*. Anti-VEGF receptor-2 monoclonal antibody prevents portal-systemic collateral vessel formation in portal hypertensive mice. *Gastroenterology* 2004;**126**:886–94.
118. Fernandez M, Mejias M, Angermayr B *et al*. Inhibition of VEGF receptor-2 decreases the development of hyperdynamic splanchnic circulation and portal-systemic collateral vessels in portal hypertensive rats. *J Hepatol* 2005;**43**:98–103.
119. Van Steenkiste C, Geerts A, Vanheule E *et al*. Role of placental growth factor in mesenteric neoangiogenesis in a mouse model of portal hypertension. *Gastroenterology* 2009;**137**: 2112–24.e1-6.
120. Van Steenkiste C, Ribera J, Geerts A *et al*. Inhibition of placental growth factor activity reduces the severity of fibrosis, inflammation, and portal hypertension in cirrhotic mice. *Hepatology* 2011;**53**:1629–40.
121. Reichenbach V, Fernandez-Varo G, Casals G *et al*. Adenoviral dominant-negative soluble PDGFRbeta improves hepatic collagen, systemic hemodynamics, and portal pressure in fibrotic rats. *J Hepatol* 2012;**57**:967–73.
122. Fernandez M, Mejias M, Garcia-Pras E *et al*. Reversal of portal hypertension and hyperdynamic splanchnic circulation by combined vascular endothelial growth factor and platelet-derived growth factor blockade in rats. *Hepatology* 2007;**46**:1208–17.
123. Mejias M, Garcia-Pras E, Tiani C *et al*. Beneficial effects of sorafenib on splanchnic, intrahepatic, and portocollateral circulations in portal hypertensive and cirrhotic rats. *Hepatology* 2009;**49**:1245–56.
124. Hennenberg M, Trebicka J, Stark C *et al*. Sorafenib targets dysregulated Rho kinase expression and portal hypertension in rats with secondary biliary cirrhosis. *Br J Pharmacol* 2009;**157**:258–70.
125. Reiberger T, Angermayr B, Schwabl P *et al*. Sorafenib attenuates the portal hypertensive syndrome in partial portal vein ligated rats. *J Hepatol* 2009;**51**:865–73.
126. Tugues S, Fernandez-Varo G, Munoz-Luque J *et al*. Antiangiogenic treatment with sunitinib ameliorates inflammatory infiltrate, fibrosis, and portal pressure in cirrhotic rats. *Hepatology* 2007;**46**:1919–26.
127. Yang YY, Liu RS, Lee PC *et al*. Anti-VEGFR agents ameliorate hepatic venous dysregulation/microcirculatory dysfunction, splanchnic venous pooling and ascites of NASH-cirrhotic rat. *Liver Int* 2014;**34**:521–34.
128. Lin HC, Huang YT, Yang YY *et al*. Beneficial effects of dual vascular endothelial growth factor receptor/fibroblast growth factor receptor inhibitor brivanib alaninate in cirrhotic portal hypertensive rats. *J Gastroenterol Hepatol* 2014;**29**: 1073–82.

129. Uschner F, Nikolova I, Klein S *et al*. The multikinase-inhibitor regorafenib improves portal hypertension in presence and absence of cirrhosis in rats. *Hepatology* 2016;**64**:1049A.
130. Qu K, Huang Z, Lin T *et al*. New Insight into the anti-liver fibrosis effect of multitargeted tyrosine kinase inhibitors: from molecular target to clinical trials. *Front Pharmacol* 2015;**6**:300.
131. D'Amico M, Mejias M, Garcia-Pras E *et al*. Effects of the combined administration of propranolol plus sorafenib on portal hypertension in cirrhotic rats. *Am J Physiol Gastrointest Liver Physiol* 2012;**302**:G1191–8.
132. Pinter M, Sieghart W, Reiberger T *et al*. The effects of sorafenib on the portal hypertensive syndrome in patients with liver cirrhosis and hepatocellular carcinoma—a pilot study. *Aliment Pharmacol Ther* 2012;**35**:83–91.
133. Coriat R, Gouya H, Mir O *et al*. Reversible decrease of portal venous flow in cirrhotic patients: a positive side effect of sorafenib. *PloS One* 2011;**6**:e16978.
134. Garcia-Tsao G, Fallon M, Reddy K *et al*. Placebo-controlled, randomized, pilot study of the effect of sorafenib on portal pressure in patients with cirrhosis, portal hypertension and ablated hepatocellular carcinoma (HCC). *Hepatology* 2015;**62**:580A.
135. Mejias M, Coch L, Berzigotti A *et al*. Antiangiogenic and antifibrogenic activity of pigment epithelium-derived factor (PEDF) in bile duct-ligated portal hypertensive rats. *Gut* 2015;**64**:657–66.
136. Coch L, Mejias M, Berzigotti A *et al*. Disruption of negative feedback loop between vasohibin-1 and vascular endothelial growth factor decreases portal pressure, angiogenesis, and fibrosis in cirrhotic rats. *Hepatology* 2014;**60**:633–47.
137. Yang L, Kwon J, Popov Y *et al*. Vascular endothelial growth factor promotes fibrosis resolution and repair in mice. *Gastroenterology* 2014;**146**:1339–50.e1.
138. Chou R, Dana T, Blazina I *et al*. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. *Jama* 2016;**316**:2008–24.
139. Sikka P, Saxena KK, Kapoor S. Statin Hepatotoxicity: Is it a real concern? *Heart Views* 2011;**12**:104–6.
140. Zafra C, Abraldes JG, Turnes J *et al*. Simvastatin enhances hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis. *Gastroenterology* 2004;**126**:749–55.
141. Noma K, Oyama N, Liao JK. Physiological role of ROCKs in the cardiovascular system. *Am J Physiol Cell Physiol* 2006;**290**:C661–8.
142. Abraldes JG, Rodriguez-Vilarrupla A, Graupera M *et al*. Simvastatin treatment improves liver sinusoidal endothelial dysfunction in CCl4 cirrhotic rats. *J Hepatol* 2007;**46**:1040–6.
143. Trebicka J, Hennenberg M, Laleman W *et al*. Atorvastatin lowers portal pressure in cirrhotic rats by inhibition of RhoA/Rho-kinase and activation of endothelial nitric oxide synthase. *Hepatology* 2007;**46**:242–53.
144. Zhou Q, Hennenberg M, Trebicka J *et al*. Intrahepatic upregulation of RhoA and Rho-kinase signalling contributes to increased hepatic vascular resistance in rats with secondary biliary cirrhosis. *Gut* 2006;**55**:1296–1305.
145. Klein S, Van Beuge MM, Granzow M *et al*. HSC-specific inhibition of Rho-kinase reduces portal pressure in cirrhotic rats without major systemic effects. *J Hepatol* 2012;**57**:1220–7.
146. Demirbilek S, Tas E, Gurunluoglu K *et al*. Fluvastatin reduced liver injury in rat model of extrahepatic cholestasis. *Pediatr Surg Int* 2007;**23**:155–62.
147. Trebicka J, Hennenberg M, Odenthal M *et al*. Atorvastatin attenuates hepatic fibrosis in rats after bile duct ligation via decreased turnover of hepatic stellate cells. *J Hepatol* 2010;**53**:702–12.
148. Klein S, Klosel J, Schierwagen R *et al*. Atorvastatin inhibits proliferation and apoptosis, but induces senescence in hepatic myofibroblasts and thereby attenuates hepatic fibrosis in rats. *Lab Invest* 2012;**92**:1440–50.
149. Marrone G, Russo L, Rosado E *et al*. The transcription factor KLF2 mediates hepatic endothelial protection and paracrine endothelial-stellate cell deactivation induced by statins. *J Hepatol* 2013;**58**:98–103.
150. Miao Q, Zeng X, Ma G *et al*. Simvastatin suppresses the proangiogenic microenvironment of human hepatic stellate cells via the Kruppel-like factor 2 pathway. *Rev Esp Enferm Dig* 2015;**107**:63–71.
151. Marrone G, Maeso-Diaz R, Garcia-Cardena G *et al*. KLF2 exerts antifibrotic and vasoprotective effects in cirrhotic rat livers: behind the molecular mechanisms of statins. *Gut* 2015;**64**:1434–43.
152. Huang HC, Wang SS, Lee JY *et al*. Simvastatin effects on portal-systemic collaterals of portal hypertensive rats. *J Gastroenterol Hepatol* 2010;**25**:1401–9.
153. Hsu SJ, Wang SS, Hsin IF *et al*. Effects of simvastatin on the portal-systemic collateral vascular response to endothelin-1 and shunting degree in portal hypertensive rats. *Scand J Gastroenterol* 2013;**48**:831–8.
154. Uschner FE, Ranabhat G, Choi SS *et al*. Statins activate the canonical hedgehog-signaling and aggravate non-cirrhotic portal hypertension, but inhibit the non-canonical hedgehog signaling and cirrhotic portal hypertension. *Sci Rep* 2015;**5**:14573.
155. Abraldes JG, Albillos A, Banares R *et al*. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. *Gastroenterology* 2009;**136**:1651–8.
156. Pollo-Flores P, Soldan M, Santos UC *et al*. Three months of simvastatin therapy vs. placebo for severe portal hypertension in cirrhosis: a randomized controlled trial. *Dig Liver Dis* 2015;**47**:957–63.
157. Abraldes JG, Villanueva C, Aracil C *et al*. Addition of simvastatin to standard therapy for the prevention of variceal rebleeding does not reduce rebleeding but increases survival in patients with cirrhosis. *Gastroenterology* 2016;**150**:1160–70.e1163.
158. Alvarado-Tapias E, Ardevol A, Pavel O *et al*. Hemodynamic effects of carvedilol plus simvastatin in cirrhosis with portal hypertension and no-response to β-blockers: a double-blind randomized trial. *Hepatology* 2016;**64**:74A.
159. Simon TG, Bonilla H, Yan P *et al*. Atorvastatin and fluvastatin are associated with dose-dependent reductions in cirrhosis and hepatocellular carcinoma, among patients with hepatitis C virus: results from ERCHIVES. *Hepatology* 2016;**64**:47–57.
160. Mohanty A, Tate JP, Garcia-Tsao G. Statins are associated with a decreased risk of decompensation and death in veterans with hepatitis C-related compensated cirrhosis. *Gastroenterology* 2016;**150**:430–40.e431.
161. Rodriguez S, Raurell I, Torres-Arauz M *et al*. A nitric oxide-donating statin decreases portal pressure with a better

toxicity profile than conventional statins in cirrhotic rats. *Scientific Reports* 2017;**7**:40461.
162. Higashiyama H, Kinoshita M, Asano S. Immunolocalization of farnesoid X receptor (FXR) in mouse tissues using tissue microarray. *Acta histochemica* 2008;**110**:86–93.
163. Halilbasic E, Fuchs C, Traussnigg S *et al*. Farnesoid X receptor agonists and other bile acid signaling strategies for treatment of liver disease. *Dig Dis* 2016;**34**:580–8.
164. Fuchs CD, Schwabl P, Reiberger T *et al*. Liver capsule: FXR agonists against liver disease. *Hepatology* 2016;**64**:1773.
165. Roda A, Pellicciari R, Gioiello A *et al*. Semisynthetic bile acid FXR and TGR5 agonists: physicochemical properties, pharmacokinetics, and metabolism in the rat. *J Pharmacol Exp Ther* 2014;**350**:56–68.
166. Hambruch E, Miyazaki-Anzai S, Hahn U *et al*. Synthetic farnesoid X receptor agonists induce high-density lipoprotein-mediated transhepatic cholesterol efflux in mice and monkeys and prevent atherosclerosis in cholesteryl ester transfer protein transgenic low-density lipoprotein receptor (-/-) mice. *J Pharmacol Exp Ther* 2012;**343**:556–67.
167. Kinzel O, Steeneck C, Schlüter T *et al*. Novel substituted isoxazole FXR agonists with cyclopropyl, hydroxycyclobutyl and hydroxyazetidinyl linkers: understanding and improving key determinants of pharmacological properties. *Bioorg Med Chem Lett* 2016;**26**:3746–53.
168. Li J, Wilson A, Kuruba R *et al*. FXR-mediated regulation of eNOS expression in vascular endothelial cells. *Cardiovasc Res* 2008;**77**:169–77.
169. Li YT, Swales KE, Thomas GJ *et al*. Farnesoid x receptor ligands inhibit vascular smooth muscle cell inflammation and migration. *Arterioscler Thromb Vasc Biol* 2007;**27**:2606–11.
170. Wang YD, Chen WD, Wang M *et al*. Farnesoid X receptor antagonizes nuclear factor kappaB in hepatic inflammatory response. *Hepatology* 2008;**48**:1632–43.
171. Fiorucci S, Antonelli E, Rizzo G *et al*. The nuclear receptor SHP mediates inhibition of hepatic stellate cells by FXR and protects against liver fibrosis. *Gastroenterology* 2004;**127**:1497–1512.
172. Baghdasaryan A, Claudel T, Gumhold J *et al*. Dual farnesoid X receptor/TGR5 agonist INT-767 reduces liver injury in the Mdr2-/- (Abcb4-/-) mouse cholangiopathy model by promoting biliary HCO(-)(3) output. *Hepatology* 2011;**54**:1303–12.
173. Zhang L, Wang YD, Chen WD *et al*. Promotion of liver regeneration/repair by farnesoid X receptor in both liver and intestine in mice. *Hepatology* 2012;**56**:2336–43.
174. Zhang S, Wang J, Liu Q *et al*. Farnesoid X receptor agonist WAY-362450 attenuates liver inflammation and fibrosis in murine model of non-alcoholic steatohepatitis. *J Hepatol* 2009;**51**:380–8.
175. Verbeke L, Farre R, Trebicka J *et al*. Obeticholic acid, a farnesoid X receptor agonist, improves portal hypertension by two distinct pathways in cirrhotic rats. *Hepatology* 2014;**59**:2286–98.
176. Mookerjee RP, Mehta G, Balasubramaniyan V *et al*. Hepatic dimethylarginine-dimethylaminohydrolase1 is reduced in cirrhosis and is a target for therapy in portal hypertension. *J Hepatol* 2015;**62**:325–31.
177. Schwabl P, Hambruch E, Seeland BA *et al*. The FXR agonist PX20606 ameliorates portal hypertension by targeting vascular remodelling and sinusoidal dysfunction. *J Hepatol* 2017;**66**:724–33.
178. Laleman W, Omasta A, Van de Casteele M *et al*. A role for asymmetric dimethylarginine in the pathophysiology of portal hypertension in rats with biliary cirrhosis. *Hepatology* 2005;**42**:1382–90.
179. Vizzutti F, Romanelli RG, Arena U *et al*. ADMA correlates with portal pressure in patients with compensated cirrhosis. *Eur J Clin Invest* 2007;**37**:509–15.
180. Renga B, Mencarelli A, Migliorati M *et al*. Bile-acid-activated farnesoid X receptor regulates hydrogen sulfide production and hepatic microcirculation. *World J Gastroenterol* 2009;**15**:2097–2108.
181. Verbeke L, Mannaerts I, Schierwagen R *et al*. FXR agonist obeticholic acid reduces hepatic inflammation and fibrosis in a rat model of toxic cirrhosis. *Sci Rep* 2016;**6**:33453.
182. Fickert P, Fuchsbichler A, Moustafa T *et al*. Farnesoid X receptor critically determines the fibrotic response in mice but is expressed to a low extent in human hepatic stellate cells and periductal myofibroblasts. *Am J Pathol* 2009;**175**:2392–2405.
183. Li J, Kuruba R, Wilson A *et al*. Inhibition of endothelin-1-mediated contraction of hepatic stellate cells by FXR ligand. *PloS One* 2010;**5**:e13955.
184. Xu W, Lu C, Zhang F *et al*. Dihydroartemisinin counteracts fibrotic portal hypertension via farnesoid X receptor-dependent inhibition of hepatic stellate cell contraction. *FEBS J* 2017;**284**:114–33.
185. Inagaki T, Moschetta A, Lee YK *et al*. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. *Proc Nat Acad Sci U S A* 2006;**103**:3920–5.
186. Verbeke L, Farre R, Verbinnen B *et al*. The FXR agonist obeticholic acid prevents gut barrier dysfunction and bacterial translocation in cholestatic rats. *Am J Pathol* 2015;**185**:409–19.
187. Ubeda M, Lario M, Munoz L *et al*. Obeticholic acid reduces bacterial translocation and inhibits intestinal inflammation in cirrhotic rats. *J Hepatol* 2016;**64**:1049–57.
188. Lutz P, Berger C, Langhans B *et al*. A farnesoid X receptor polymorphism predisposes to spontaneous bacterial peritonitis. *Dig Liver Dis* 2014;**46**:1047–50.
189. Schwabl P, Hambruch E, Supper P *et al*. The non-steroidal fxr agonist GS-9674 reduces liver fibrosis and ameliorates portal hypertension in a rat NASH model. *J Hepatol* 2016;**64**:S165.
190. Mookerjee R, Rosselli M, Pieri G *et al*. Effects of the FXR agonist obeticholic acid on hepatic venous pressure gradient (HVPG) in alcoholic cirrhosis: a proof of concept phase 2a study. *J Hepatol* 2014;**60**:S7.
191. Neuschwander-Tetri BA, Loomba R, Sanyal AJ *et al*. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet* 2015;**385**:956–65.
192. Laleman W, Landeghem L, Wilmer A *et al*. Portal hypertension: from pathophysiology to clinical practice. *Liver Int* 2005;**25**:1079–90.
193. Paternostro R, Reiberger T, Mandorfer M *et al*. Plasma renin concentration represents an independent risk factor for mortality and is associated with liver dysfunction in patients with cirrhosis. *J Gastroenterol Hepatol* 2017;**32**:184–90.
194. Tandon P, Abraldes JG, Berzigotti A *et al*. Renin-angiotensin-aldosterone inhibitors in the reduction of portal pressure: a systematic review and meta-analysis. *J Hepatol* 2010;**53**:273–82.
195. Sen S, De BK, Biswas PK *et al*. Hemodynamic effect of spironolactone in liver cirrhosis and propranolol-resistant portal hypertension. *Indian J Gastroenterol* 2002;**21**:145–8.

196. Schepke M, Wiest R, Flacke S *et al*. Irbesartan plus low-dose propranolol versus low-dose propranolol alone in cirrhosis: a placebo-controlled, double-blind study. *Am J Gastroenterol* 2008;**103**:1152–8.
197. Kim JH, Kim JM, Cho YZ *et al*. Effects of candesartan and propranolol combination therapy versus propranolol monotherapy in reducing portal hypertension. *Clin Mol Hepatol* 2014;**20**:376–83.
198. Abecasis R, Kravetz D, Fassio E *et al*. Nadolol plus spironolactone in the prophylaxis of first variceal bleed in nonascitic cirrhotic patients: a preliminary study. *Hepatology* 2003;**37**:359–65.
199. Bataller R, Gines P, Nicolas JM *et al*. Angiotensin II induces contraction and proliferation of human hepatic stellate cells. *Gastroenterology* 2000;**118**:1149–56.
200. Bataller R, Sancho-Bru P, Gines P *et al*. Activated human hepatic stellate cells express the renin-angiotensin system and synthesize angiotensin II. *Gastroenterology* 2003;**125**:117–25.
201. Afroze SH, Munshi MK, Martinez AK *et al*. Activation of the renin-angiotensin system stimulates biliary hyperplasia during cholestasis induced by extrahepatic bile duct ligation. *Am J Physiol Gastrointest Liver Physiol* 2015;**308**:G691–701.
202. Bataller R, Gabele E, Parsons CJ *et al*. Systemic infusion of angiotensin II exacerbates liver fibrosis in bile duct-ligated rats. *Hepatology* 2005;**41**:1046–55.
203. Moreno M, Gonzalo T, Kok RJ *et al*. Reduction of advanced liver fibrosis by short-term targeted delivery of an angiotensin receptor blocker to hepatic stellate cells in rats. *Hepatology* 2010;**51**:942–52.
204. Luo W, Meng Y, Ji HL *et al*. Spironolactone lowers portal hypertension by inhibiting liver fibrosis, ROCK-2 activity and activating NO/PKG pathway in the bile-duct-ligated rat. *PloS One* 2012;**7**:e34230.
205. Debernardi-Venon W, Martini S, Biasi F *et al*. AT1 receptor antagonist Candesartan in selected cirrhotic patients: effect on portal pressure and liver fibrosis markers. *J Hepatol* 2007;**46**:1026–33.
206. Corey KE, Shah N, Misdraji J *et al*. The effect of angiotensin-blocking agents on liver fibrosis in patients with hepatitis C. *Liver Int* 2009;**29**:748–53.
207. Colmenero J, Bataller R, Sancho-Bru P *et al*. Effects of losartan on hepatic expression of nonphagocytic NADPH oxidase and fibrogenic genes in patients with chronic hepatitis C. *Am J Physiol Gastrointest Liver Physiol* 2009;**297**:G726–34.
208. Kim MY, Cho MY, Baik SK *et al*. Beneficial effects of candesartan, an angiotensin-blocking agent, on compensated alcoholic liver fibrosis—a randomized open-label controlled study. *Liver Int* 2012;**32**:977–87.
209. Abu Dayyeh BK, Yang M, Dienstag JL *et al*. The effects of angiotensin blocking agents on the progression of liver fibrosis in the HALT-C Trial cohort. *Dig Dis Sci* 2011;**56**:564–8.
210. Klein S, Rick J, Lehmann J *et al*. Janus-kinase-2 relates directly to portal hypertension and to complications in rodent and human cirrhosis. *Gut* 2017;**66**:145–55.
211. Granzow M, Schierwagen R, Klein S *et al*. Angiotensin-II type 1 receptor-mediated Janus kinase 2 activation induces liver fibrosis. *Hepatology* 2014;**60**:334–48.
212. Wang D, Yin J, Dong R *et al*. Inhibition of Janus kinase-2 signalling pathway ameliorates portal hypertensive syndrome in partial portal hypertensive and liver cirrhosis rats. *Dig Liver Dis* 2015;**47**:315–23.
213. Wang D, Wang Q, Yin J *et al*. Combined administration of propranolol + AG490 offers better effects on portal hypertensive rats with cirrhosis. *J Gastroenterol Hepatol* 2016;**31**:1037–44.
214. Jiang F, Yang J, Zhang Y *et al*. Angiotensin-converting enzyme 2 and angiotensin 1–7: novel therapeutic targets. *Nat Rev Cardiol* 2014;**11**:413–26.
215. Herath CB, Warner FJ, Lubel JS *et al*. Upregulation of hepatic angiotensin-converting enzyme 2 (ACE2) and angiotensin-(1–7) levels in experimental biliary fibrosis. *J Hepatol* 2007;**47**:387–95.
216. Lubel JS, Herath CB, Tchongue J *et al*. Angiotensin-(1–7), an alternative metabolite of the renin-angiotensin system, is up-regulated in human liver disease and has antifibrotic activity in the bile-duct-ligated rat. *Clin Sci* 2009;**117**:375–86.
217. Grace JA, Klein S, Herath CB *et al*. Activation of the MAS receptor by angiotensin-(1–7) in the renin-angiotensin system mediates mesenteric vasodilatation in cirrhosis. *Gastroenterology* 2013;**145**:874–84.e5.
218. Herath CB, Mak K, Burrell LM *et al*. Angiotensin-(1–7) reduces the perfusion pressure response to angiotensin II and methoxamine via an endothelial nitric oxide-mediated pathway in cirrhotic rat liver. *Am J Physiol Gastrointest Liver Physiol* 2013;**304**:G99–108.
219. Klein S, Herath CB, Schierwagen R *et al*. Hemodynamic effects of the non-peptidic angiotensin-(1–7) agonist AVE0991 in liver cirrhosis. *PloS One* 2015;**10**:e0138732.
220. Dahl E, Gluud LL, Kimer N *et al*. Meta-analysis: the safety and efficacy of vaptans (tolvaptan, satavaptan and lixivaptan) in cirrhosis with ascites or hyponatraemia. *Aliment Pharmacol Ther* 2012;**36**:619–26.
221. https://clinicaltrials.gov/ct2/show/NCT00592475 and http://www.clinicaltrialsregister.eu/ctr-search/trial/2007–001661–15/ES.
222. Fernandez-Varo G, Oro D, Cable EE *et al*. Vasopressin 1a receptor partial agonism increases sodium excretion and reduces portal hypertension and ascites in cirrhotic rats. *Hepatology* 2016;**63**:207–16.
223. https://clinicaltrials.gov/ct2/show/NCT02929407.
224. Garcia-Compean D, Jaquez-Quintana JO, Gonzalez-Gonzalez JA *et al*. Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. *World J Gastroenterol* 2009;**15**:280–8.
225. Amodio P, Bemeur C, Butterworth R *et al*. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. *Hepatology* 2013;**58**:325–36.
226. Tripathi DM, Erice E, Lafoz E *et al*. Metformin reduces hepatic resistance and portal pressure in cirrhotic rats. *Am J Physiol Gastrointest Liver Physiol* 2015;**309**:G301–9.
227. Mesquita F, Guixe-Muntet S, Fernandez-Iglesias A *et al*. Liraglutide deactivates hepatic stellate cells improving liver microvascular dysfunction and fibrosis in rats with chronic liver disease. *Hepatology* 2016;**64**:83A.
228. Schwabl P, Payer BA, Grahovac J *et al*. Pioglitazone decreases portosystemic shunting by modulating inflammation and angiogenesis in cirrhotic and non-cirrhotic portal hypertensive rats. *J Hepatol* 2014;**60**:1135–42.
229. Rodriguez-Vilarrupla A, Lavina B, Garcia-Caldero H *et al*. PPARalpha activation improves endothelial dysfunction and reduces fibrosis and portal pressure in cirrhotic rats. *J Hepatol* 2012;**56**:1033–9.
230. Delgado MG, Gracia-Sancho J, Marrone G *et al*. Leptin receptor blockade reduces intrahepatic vascular resistance and

portal pressure in an experimental model of rat liver cirrhosis. *Am J Physiol Gastrointest Liver Physiol* 2013;**305**:G496–502.
231. Trebicka J, Racz I, Siegmund SV *et al*. Role of cannabinoid receptors in alcoholic hepatic injury: steatosis and fibrogenesis are increased in CB2 receptor-deficient mice and decreased in CB1 receptor knockouts. *Liver Int* 2011;**31**:860–70.
232. Steib CJ, Gmelin L, Pfeiler S *et al*. Functional relevance of the cannabinoid receptor 2–heme oxygenase pathway: a novel target for the attenuation of portal hypertension. *Life Sci* 2013;**93**:543–51.
233. Huang HC, Wang SS, Hsin IF *et al*. Cannabinoid receptor 2 agonist ameliorates mesenteric angiogenesis and portosystemic collaterals in cirrhotic rats. *Hepatology* 2012;**56**:248–58.
234. Reichenbach V, Ros J, Fernandez-Varo G *et al*. Prevention of fibrosis progression in CCl4-treated rats: role of the hepatic endocannabinoid and apelin systems. *J Pharmacol Exp Ther* 2012;**340**:629–37.
235. Yang YY, Hsieh SL, Lee PC *et al*. Long-term cannabinoid type 2 receptor agonist therapy decreases bacterial translocation in rats with cirrhosis and ascites. *J Hepatol* 2014;**61**:1004–13.
236. Hsu SJ, Lee FY, Wang SS *et al*. Caffeine ameliorates hemodynamic derangements and portosystemic collaterals in cirrhotic rats. *Hepatology* 2015;**61**:1672–84.
237. De Gottardi A, Berzigotti A, Seijo S *et al*. Postprandial effects of dark chocolate on portal hypertension in patients with cirrhosis: results of a phase 2, double-blind, randomized controlled trial. *Am J Clin Nutr* 2012;**96**:584–90.
238. Di Pascoli M, Divi M, Rodriguez-Vilarrupla A *et al*. Resveratrol improves intrahepatic endothelial dysfunction and reduces hepatic fibrosis and portal pressure in cirrhotic rats. *J Hepatol* 2013;**58**:904–10.
239. Liang J, Deng X, Lin ZX *et al*. Attenuation of portal hypertension by natural taurine in rats with liver cirrhosis. *World J Gastroenterol* 2009;**15**:4529–37.
240. Schwarzer R, Paternostro R, Mandorfer M *et al*. Taurine lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized, placebo controlled, double blind pilot study. *Hepatology* 2015;**62**:284A.