Pharmacological management of portal hypertension: current status and future

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Portal hypertension (PHT) is the trigger of the severe complications of cirrhosis, including esophagogastric variceal bleeding (EVB), ascites, hepatic encephalopathy, cirrhotic cardiomyopathy, acute kidney injury and hepatorenal syndrome (AKI-HRS), which may cause death or increase the need for liver transplantation.[1,2] Of these, EVB remains one of the deadliest complications of PHT. As of now, the most widely accepted measure to assess portal pressure (PP) and PHT is the hepatic venous pressure gradient (HVPG) via transjugular-hepatic vein balloon catheterization.[3] The pharmacological management of PHT aims to reduce PP and prevent PHT-related complications.[4,5] Given that PP is determined by portal blood flow and hepatic vascular resistance,[4] currently used drugs are mainly targeted to modulate the increased liver blood flow, such as reducing hyperdynamic circulation, renin-angiotensin-aldosterone system activation, vascular hyperplasia, and collateral circulation formation, or decrease intravascular resistance, such as inhibiting liver fibrosis, regenerative nodules, and angiogenesis.[6] In the setting of PHT, arterial vasodilation occurs both in the splanchnic and systemic circulation, therefore, activates the neurohumoral and vasoconstrictive systems, which leads to sodium and water retention, increased blood volume, and increased cardiac output.[7] Terlipressin, somatostatin (SMT) or octreotide, and non-selective β-blockers (NSBBs) decrease the portal venous inflow through splanchnic vasoconstriction. However, the cross-talk between vasoactive substances and contractile cells often leads to abnormal liver microcirculation and PHT development.[6] Those may be new targets for the pharmacological management of PHT in the future.

In clinical practice, SMT and octreotide are usually used to treat PHT-induced acute variceal bleeding (AVB) independently or combined with urgent endoscopic therapy [Table 1].[8-10] A meta-analysis of 30 randomized controlled trials comprising in total of 3344 patients indicated that terlipressin combined with endoscopic variceal ligation had a lower 5-day treatment failure rate and transfusion requirement than terlipressin alone.[11] Furthermore, the combination of SMT/octreotide and endoscopic therapy is effective in controlling AVB.[12] The efficacy of these drugs combined with α-adrenergic receptors activators, such as noradrenaline and midodrine, have also been evaluated in the treatment of AKI-HRS.[3,9] Recent evidence suggests that the efficacy of terlipressin with albumin is superior to midodrine combined with octreotide. The use of terlipressin and albumin in a timely fashion significantly improves AKI-HRS in cirrhotic patients with ascites.[13,14] This approach is also as effective as noradrenaline to reverse AKI-HRS in cirrhotic patients with PHT. [12,14]

As the mainstream drugs for long-term treatment in cirrhotic patients with PHT, NSBBs are used to prevent the primary and secondary EVB and reduce the risk of hepatic decompensation.[15] However, only 30% to 40% of patients treated with long-term NSBBs achieve a response to reduce HVPG. Also, NSBBs may lead to undesirable outcomes, for example, portal vein thrombosis (PVT), AKI, in a portion of cirrhotic patients (odds ratio 4.62, 95% confidence interval 2.50–8.53; $P < 0.001$) due to remarkably decreased portal vein velocity.[15] Although carvedilol treatment achieves a good hemodynamic response in propranolol non-responders, it may break the delicate hemodynamic balance in cirrhotic patients and increase mortality.[16]

To date, multiple new drugs, including statins, anticoagulants, pioglitazone, sorafenib, PX20606, tetrahydrobiopterin, antioxidants, or supplementary treatment such as caffeine and green tea polyphenol, have been reported to benefit PHT patients or animal models. Among

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Table 1: Clinical practice guidelines for the management of esophagogastric variceal bleeding in cirrhotic patients with portal hypertension.

Drugs	Guidelines	Characteristics and main mechanisms	Recommended dosage
Telipressin	China (2016) [8] EASL (2018) [9]	Long-acting synthetic analogue of vasopressin, splanchnic vasoconstrictor	Initially a 1 mg bolus injection, then a bolus of 1–2 mg every 4–6 h depending on patient tolerated and their co-morbidities (more side effects) or continuous intravenous infusion of 1–2 mg every 6 h (well-tolerated), the maximal dosage, 12 mg/day, 3–5 days.
SMT	China (2016)[8] EASL (2018) [9] AASLD (2016) [10]	Nature SMT, inhibit the release of vasodilatory peptides	A bolus of 500 μg injection, then continuous intravenous infusion of 250–500 μg/h, 3–5 days.
Octreotide	China (2016)[8] EASL (2018) [9] AASLD (2016) [10]	Long half-life time synthetic analogue of SMT with the same mechanisms	A bolus of 100 μg, then continuous intravenous infusion of 25–50 μg/h, 3–5 days.
NSBBs	China (2016)[8] EASL (2018)[9] AASLD (2016)[10]	β-1 and β-2 adrenergic receptor antagonist, long-time treatment for cirrhotic patients with PHT	Propranolol: 20–40 mg/day; adding dosage of 10–20 mg every 2–3 days; usually maximal dosage of 80 mg/day. Nadolol (long-acting NSBBs): 20–40 mg qd, usually maximal dosage of 80 mg/d. Carvedilol (not only decreases portal flow but also reduces intrahepatic resistance): 6.25 mg qd, the maximal dosage, 25 mg/day (except persistent hypertension).

SMT: Somatostatin; NSBBs: Non-selective β-blockers; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases; qd: Once a day.

them, statins are promising in dealing with PHT in the setting of non-alcoholic steatohepatitis related cirrhosis, by improving liver sinusoidal endothelial cells function and reducing intrahepatic resistance through inhibition of Rho-associated kinase signaling and activation of endothelial nitric oxide synthase.[17] Besides statins, low-molecular-weight heparin or direct-acting anticoagulants (DOACs) are capable of increasing PVT recanalization without extra bleeding and decreasing the incidence of EVB in cirrhotic patients with PVT.[18] Moreover, an observational study shows that DOACs are safe and effective in preventing PVT, delaying hepatic decompensation, and improving prognosis in patients with cirrhosis.[12] It is suggested that DOACs may be safe and effective in patients with compensated cirrhosis. However, further studies are needed to determine the optimal type of anticoagulant and dose in patients with compensated and decompensated cirrhosis.

Non-cirrhotic portal hypertension (NCPH) is a disease entity due to rare hepatic sinus-portal vascular diseases or systemic diseases. NCPH is characterized by normal liver function, normal or low HVPG, ascites, splenomegaly, and easily occurrence of EVB. It is noteworthy that NCPH can be easily misdiagnosed as cirrhotic portal hypertension. For NCPH-induced EVB, endoscopic and drug therapies are safe and effective in current clinical practice.[19,20]

In summary, pharmacological management is the mainstay of PHT in cirrhotic or NCPH patients. Terlipressin, SMT, and octreotide are the first-line drugs for treating AVB in patients with PHT. Propranolol and carvedilol are recommended for the long-term treatment of cirrhotic PHT. Whether these drugs, especially NSBBs, are also safe and efficient in NCPH patients requires further investigation. Novel therapeutic drugs, which could effectively reduce PP, are needed in clinical practice.

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Conflicts of interest

None.

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