Antihepatic Fibrosis Drugs in Clinical Trials

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Abstract

Liver fibrosis is not an independent disease. It refers to the abnormal proliferation of connective tissues in the liver caused by various pathogenic factors. Thus far, liver fibrosis has been considered to be associated with a set of factors, such as viral infection, alcohol abuse, non-alcoholic fatty liver disease, and autoimmune hepatitis, as well as genetic diseases. To date, clinical therapeutics for liver fibrosis still face challenges, as elimination of potential causes and conventional antifibrotic drugs cannot alleviate fibrosis in most patients. Recently, potential therapeutic targets of liver fibrosis, such as metabolism, inflammation, cell death and the extracellular matrix, have been explored through basic and clinical research. Therefore, it is extremely urgent to review the antihepatic fibrosis therapeutics for treatment of liver fibrosis in current clinical trials.

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Introduction

Hepatic fibrosis, a reversible response to various chronic liver injuries, may progress to cirrhosis, hepatocellular carcinoma and liver failure. Cirrhosis is the common end-stage of a series of chronic liver diseases and can be divided according to its compensated and decompensated states. A series of complications of cirrhosis (such as portal hypertension, infection, ascites, and esophageal bleeding) are associated with significant morbidity and mortality.

The mechanism involved in the progression and reversal of liver fibrosis is still not clear. Up to now, alcohol, hepatocyte lipid deposition, and insulin resistance (IR) are recognized to be the major risk factors in patients with chronic hepatitis.

Keywords: Liver fibrosis; Therapeutics; Clinical trial; Cholestatic liver diseases; Non-alcoholic steatohepatitis.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ALD, alcoholic liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASK1, apoptosis signal-regulating kinase 1; CLD, cholestatic liver diseases; CVC, cenicriviroc; ECM, extracellular matrix; FGF, fibroblast growth factor; FXR, farnesoid X nuclear receptor; HSC, hepatic stellate cell; IR, insulin resistance; LOX, lysyl oxidase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OA, oleic acid; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; TG, triglyceride; TGF-β, transforming growth factor β; UDCA, ursodeoxycholic acid.

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Besides, intrahepatic oxidative stress, viral and schistosomiasis infection, hepatic sinus microcirculation disturbance, and microbiota dysbiosis also participate in the occurrence and development of liver fibrosis.

Current therapies for liver fibrosis encompass two aspects: etiology treatments and antifibrotic therapeutics. Removal of underlying etiology of liver injury makes liver fibrosis reversible. However, up to now, there is lack of cause-specific treatment for certain liver diseases, such as non-alcoholic fatty liver disease (NAFLD), cholestatic liver diseases (CLDs), and some genetic liver diseases. Therefore, there remains a need to develop direct antifibrotic therapies for liver fibrosis.

Over the past several decades, many researchers have proposed potential targets and alternative therapies for liver cirrhosis. Unfortunately, there is no effective antifibrotic drug approved for human use, up to now. This review will focus on the representative drugs for liver fibrosis in clinical trials.

Pathogenesis of hepatic fibrosis

Fibrosis in epithelial organs is produced by the reticular deposition of extracellular matrix (ECM) and chronic inflammation, accompanied by compromised immune systems and pathological angiogenesis. Liver fibrosis is an abnormal perpetuation of fibrogenesis due to various constant chronic liver injuries. Apoptosis of liver parenchymal cells and continuous accumulation of ECM gradually replace the liver parenchyma with scar tissue, eventually forming liver architectural distortion, cirrhosis, portal hypertension, liver cancer, and liver failure.

As illustrated in Fig. 1, activation of hepatic stellate cells (HSCs) is well established as the central driver of hepatic fibrosis. HSCs are derived from embryonic mesothelial cells. Quiescent HSCs mainly store vitamin A and produce type IV collagen, while activated HSCs produce collagen type I, III and other proteins (fibronectin, elastin, laminin) after liver injuries. In addition, activated HSCs exhibit a developed proliferative phenotype and contractile function. Abundant ECM deposition and collagen production result in the increase of liver stiffness, thereby stimulating the activation of HSCs and forming a positive feedback loop to develop cirrhosis.3,4

Besides HSCs, other liver cells also contribute to matrix protein production. Hepatocytes, sinusoidal endothelial cells, and lymphocytes are involved in the development of liver fibrosis through releasing cell contents and cytokines.1 Macrophages in the liver comprise Kupffer cells and monocyte-derived macrophages, and the latter stimulates HSCs to become collagen-producing myofibroblasts.5

Compelling evidence from animal models indicates that liver fibrosis is reversible. Firstly, modifications in ECM composition may regulate cellular functions partly through...
cell adhesion molecules and participate in the regression of fibrosis.\textsuperscript{1,6,7} Secondly, cell death not only induces inflammation and promotes fibrogenesis but may also contribute to fibrosis resolution through influencing the apoptosis and senescence of activated HSCs.\textsuperscript{6} Lastly, infiltrating macrophages play a detrimental role in liver fibrosis. Infiltrating macrophages have shown profibrogenic and proinflammatory features in the progression of fibrosis. However, in a murine model of hepatic fibrosis, the increased restorative macrophages are associated with the accelerated resolution of fibrosis.\textsuperscript{8} Overall, the resolution of liver fibrosis is also a complex process.

**Cause-specific treatments for liver fibrosis**

Currently, the most important treatment is controlling the underlying cause of the liver diseases. These include effective suppression or elimination of hepatitis virus replication (hepatitis B virus and hepatitis C virus), drug eradication of schistosomiasis, relieving cholestasis, reduction of body weight in NAFLD, improvement of associated metabolic disorders, cessation of alcohol use in patients with alcoholic liver disease (ALD), phlebotomy in hemochromatosis, and use of corticosteroids/immunosuppressants for autoimmune liver disease. All these therapies can reduce persistent hepatic injury, thereby inhibiting liver fibrogenesis and/or promoting fibrolysis.

Many researchers demonstrated that effective inhibition of hepatitis B virus or hepatitis C virus replication significantly improved the fibrosis stage in patients with hepatitis B or C, and that liver fibrosis can be reversed in some participants.\textsuperscript{9–11} However, there are still some patients with virological and biochemical attenuation, whose liver fibrosis still exists and even progresses, eventually into liver cancer.\textsuperscript{12} Additionally, it takes a prolonged period of time to promote the resolution of liver fibrosis after viral elimination. Antiviral benefits may be offset by the increased rates of drug resistance over time.\textsuperscript{11}

Treatment based on the etiology may not completely attenuate all fibrosis patients, as there are currently no effective managements for eliminating the cause of certain liver diseases, such as autoimmune hepatitis.\textsuperscript{12} Thus, direct antifibrotic therapies targeting ECM metabolism and HSC activation are indispensable.

**Antifibrotic therapies**

Liver fibrosis plays an important role in liver tissue repair in the early stage of injury. However, the management of liver fibrosis is required in significant or advanced fibrosis and cirrhosis. At present, there is no recognized and effective antifibrotic agent. Chronic inflammatory response is the premise of fibrogenesis and the driving force of fibrotic progression. Antiinflammation, hepatocyte protection and antioxidation are important methods for hepatic fibrosis. In the following sections, we mainly review representative drugs based on therapeutic targets. Table 1 displays phase II/III/IV clinical trials for current therapies.

**Bile acid homeostasis and energy metabolism**

**Ursodeoxycholic acid**

CLDs represent a series of hepatobiliary diseases accompanied by disorders of bile formation, secretion, and excretion. The CLDs mainly include primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), both having a risk of progression to liver fibrosis. Ursodeoxycholic acid (UDCA), a physiologic hydrophilic dihydroxy bile acid, is the primary drug for treating CLD. Its antifibrotic property may be associated with the stimulation of bile secretion and the suppression of inflammation.\textsuperscript{13} Parés et al.\textsuperscript{14} pointed out that UDCA (15 mg/kg daily, 1.5-14 years) improved survival...
| NCT         | Phase | Status           | Drug       | Target                  | Population (n) | Primary endpoints                      |
|-------------|-------|------------------|------------|-------------------------|----------------|----------------------------------------|
| NCT01510860 | Phase IV | Completed | UDCA | Bile acid               | PBC (65)       | Biochemical response                   |
| NCT03345589 | Phase IV | Unknown | UDCA | Bile acid               | refractory PBC (40) | Biochemical response                  |
| NCT00550862 | Phase II | Completed | INT-747 | FXR agonist              | PBC (165)  | Biochemical response                   |
| NCT01473524 | Phase III | Completed | Obeticholic acid | FXR agonist | PBC (217) | Biochemical response                   |
| NCT00570765 | Phase II | Completed | INT747 | FXR agonist              | PBC (59)      | Biochemical response                   |
| NCT02516605 | Phase II | Completed | Tropifexor | FXR agonist | PBC (61)  | Biochemical response                   |
| NCT04065841 | Phase II | Suspended (COVID-19 pandemic) | Tropifexor | FXR agonist | NASH (210) | Histological improvements              |
| NCT03517540 | Phase II | Recruiting | Tropifexor | FXR agonist | NASH (200) | Adverse events                         |
| NCT02943460 | Phase II | Completed | Cilofexor | FXR agonist              | PSC (52)      | Adverse events                         |
| NCT02854605 | Phase II | Completed | Cilofexor | FXR agonist              | NASH (140)    | Adverse events                         |
| NCT01654731 | Phase III | Completed | Bezafibrate | PPAR agonist | Refractory PBC (100) | Biochemical response                   |
| NCT02937012 | Phase III | Unknown | Bezafibrate | PPAR agonist | Refractory PBC (34) | Biochemical response                   |
| NCT02823353 | Phase III | Unknown | Fenofibrate | PPAR agonist | PBC (200)  | Biochemical response                   |
| NCT02955602 | Phase II | Unknown | Seladelpar | PPAR agonist | Refractory PBC (116) | Biochemical response and adverse events |
| NCT02217475 | Phase II | Completed | Cenicriviroc | Dual antagonists of chemokine receptors CCR2 and CCR5 | NASH (289) | Histological improvements              |
| NCT02462967 | Phase II | Completed | GR-MD-02 | Galectin-3 inhibitor     | NASH (162)    | HVPG                                   |
| NCT02443116 | Phase II | Active, not recruiting | NGM282 | FGF19 analogs | NASH (250) | Liver fat content                      |
| NCT02413372 | Phase II | Completed | BMS-986036 | FGF21 analogs | NASH (184) | Liver fat content and adverse events   |
| NCT03486912 | Phase II | Active, not recruiting | BMS-986036 | FGF21 analogs | NASH and liver fibrosis (152) | Histological improvements |

(continued)
| NCT       | Phase | Status                | Drug                  | Target                                      | Population (n) | Primary endpoints                                      |
|-----------|-------|-----------------------|-----------------------|---------------------------------------------|----------------|--------------------------------------------------------|
| NCT03486899 | Phase II | Active, not recruiting | BMS-986036           | FGF21 analogs                              | NASH (160)     | Histological improvements                              |
| NCT03053063 | Phase III | Terminated             | Selonsertib           | Apoptosis signal-regulating kinase 1 inhibitor | NASH (883)     | Histological improvements and Event-Free Survival     |
| NCT02230670 | Phase II | Completed             | Emricasan             | Inhibitor of pan-caspase                    | Cirrhosis with MELD between 11-18 (87) | Change in cCK18/M30                                  |
| NCT03205345 | Phase II | Active, not recruiting | Emricasan             | Inhibitor of pan-caspase                    | NASH-related cirrhosis (210) | Event-free survival                                   |
| NCT02161952 | Phase II | Completed             | Pirfenidone           | Inhibitor of TGF-β                          | Chronic hepatitis C (150) | Histological improvements                              |
| NCT04099407 | Phase II | Recruiting            | Pirfenidone           | Inhibitor of TGF-β                          | Advanced cirrhosis (100) | Histological improvements                              |
| NCT02499562 | Phase II | Unknown               | Hydronidone           | Inhibitor of TGF-β                          | Chronic hepatitis B (240) | Histological improvements                              |
| NCT01672866 | Phase II | Terminated            | Simtuzumab            | LOXL2 antibody                              | NASH-related cirrhosis (222) | Histological improvements                              |
| NCT01672879 | Phase II | Terminated            | Simtuzumab            | LOXL2 antibody                              | NASH-related cirrhosis (259) | HVPG and Event-Free Survival                           |
| NCT01707472 | Phase II | Completed            | Simtuzumab            | LOXL2 antibody                              | HIV-hepatitis C virus coinfected cirrhosis (18) | Adverse events                                        |
| NCT01672853 | Phase II | Completed            | Simtuzumab            | LOXL2 antibody                              | PSC (235)      | Histological improvements                              |
| NCT00990639 | Phase II | Completed            | Candesartan           | Angiotensin receptor blocker                | Alcoholic liver fibrosis (85) | Histological improvements                              |
| NCT03770936 | Phase III | Recruiting          | Candesartan and ramipril | Angiotensin receptor blocker and angiotensin-converting enzyme inhibitor | Chronic hepatitis C (45) | FibroScan or APRI score                                |

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; HVPG, hepatic venous pressure gradient; PPAR, peroxisome proliferators-activated receptor.
Farnesoid X receptor agonist

Farnesoid X nuclear receptor (FXR), also known as bile acid receptor, is involved in the synthesis, secretion and resorption of bile acids. FXR activation effectively improves lipid metabolism through improving insulin sensitivity, decreasing hepatic gluconeogenesis, and reducing circulating triglycerides. Thus, FXR is a potential target for non-alcoholic steatohepatitis (NASH) and CLD-related liver fibrosis.

Obeticholic acid (OCA), an agonist of FXR, decreases bile acids synthesis and exerts antiinflammatory and antifibrotic effects. In a multicenter, randomized, placebo-controlled trial, patients with NASH exhibited improvements of liver histological features after treatment with OCA (25 mg, 72 weeks). However, OCA therapy was accompanied by a deterioration involving dyslipidemia and IR, indicating an increased risk of atherogenesis. Given these adverse events, OCA treatment for NASH should be further evaluated in long-term prospective trials.

OCA has also been widely used in clinical trials for PBC. Nevens et al. conducted a phase III clinical trial in PBC patients with inadequate response to conventional drugs. After 12 months of therapy, the OCA had significantly reduced ALP, high-density lipoprotein, and total bilirubin levels. These effects were sustained for 2 years. Although improvements were observed at the lower dose (5 mg) in some patients, incremental benefits occurred with adjustment to the higher dosage (10 mg). Another double-blind phase II trial, including 165 patients with inadequate response to UDCA, showed that OCA resulted in a clinically significant reduction in ALP at all doses (10, 25, and 50 mg). There were also significant improvements in gamma-glutamyltransferase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and conjugated bilirubin levels. In 2016, OCA was approved by the Food and Drug Administration for patients intolerant or with a null response to UDCA.

Dose-dependent pruritus was the only clinical adverse event that differed between OCA treatment and placebo. Pruritus can be controlled by antipruritic agents or temporary OCA interruption, but high OCA doses may result in the discontinuation due to pruritus. The mechanism of cholestatic pruritus may be related to the activation of TGR5, as OCA is a weak TGR5 agonist.

Non-bile acid FXR agonists have also been developed and are expected to cause less pruritus than OCA. Tropifexor (also known as LJN-452), a well-tolerated FXR agonist, is suitable for once-daily dosing and has been used in phase II clinical trials for PBC and NASH (NCT02516605, NCT04065841, and NCT03517540). Similarly, clofexor (otherwise known as GS-9674) is also currently undergoing phase II trials for NASH and CLD. Clofexor therapy (30 mg or 100 mg daily, 12 weeks) reduced ALP levels in a dose-dependent manner in patients with PSC, while adverse events (pruritus) were similar among groups. In another trial, clofexor (30 mg or 100 mg daily, 24 weeks) significantly improved hepatic steatosis and liver biochemistry in patients with NASH. However, no significant improvements in liver stiffness were observed with magnetic resonance imaging-proton density fat fraction and magnetic resonance elastography. Pruritus was more common in patients receiving clofexor at 100 mg than those receiving clofexor at 30 mg or placebo. Additional studies of clofexor in NASH with a longer duration are warranted.

PPAR agonist

PPAR is a key regulator of lipid metabolism in the liver and has been approved by the Food and Drug Administration as a molecular target for dyslipidemia. As distinct PPAR isoforms, PPARα regulates cholesterol and bile acid homeostasis, while PPARγ contributes to inhibiting the activation of HSCs and reducing collagen production. Hence, PPAR is a potential target for hepatic fibrosis.

Bezafibrate, an agonist of PPAR, is a widely used anti-hyperlipidemic agent. In a phase III clinical trial, bezafibrate treatment (400 mg, 24 months) in addition to UDCA contributed to a significant biochemical attenuation in PBC patients with an inadequate response to UDCA. The bezafibrate group also exhibited decreased liver stiffness and improved fibrosis scores compared with placebo. Another prospective study has compared the long-term efficacy between combination therapy (UDCA + bezafibrate) and UDCA monotherapy for PBC patients. The combination therapy significantly decreased ALP levels and Mayo risk scores but did not improve the survival rate. Bezafibrate may result in dose reduction or discontinuation due to the renal dysfunction or muscle pain.

Other PPAR agonists such as fenofibrate and seladelpar have also been used in phase II/III clinical trials (Table 1). According to a meta-analysis, combination therapy of UDCA and fenofibrate had a superior efficacy to UDCA monotherapy in reducing ALP levels, whereas no improvements were observed in clinical symptoms. No significant differences were observed in the incidence of adverse events. However, all trials included in this meta-analysis had a small sample size and no adequate histological results were reported. In prior studies, several serious adverse events were found after fibrates therapy, including hepatotoxicity, elevated creatinine, and increased creatinine kinase. Hence, larger controlled multicenter studies are required to confirm the long-term efficacy and safety of PPAR agonists.
Hepatic inflammation

**Cenicriviroc**

Approaches directly targeting the inflammatory recruitment are also important. CCR2 and its ligand are significantly increased in liver fibrosis, and fibrosis is significantly ameliorated in CCR2-deficient mice, suggesting that CCR2 is involved in liver fibrosis. CCR5 is also associated with the accumulation of collagen and ECM. Therefore, inhibition of CCRs may be a novel approach for liver fibrosis.

Cenicriviroc (CVC), an oral antagonist of the dual CCR2/CCR5 receptor, is safe, well-tolerated and has been used in phase II clinical trials in NASH patients with liver fibrosis. CVC (150 mg daily, 2 years) can significantly promote NASH regression and decrease the collagen area (as detected by morphometry on liver biopsy). Treatment benefits were more significant in patients with higher disease activity and fibrosis stage at baseline. Safety and tolerability of CVC were comparable to placebo, and adverse events (fatigue, diarrhea) had a mild or moderate severity. Another phase III trial (NCT03028740) has been posted which investigates the long-term efficacy and safety of CVC in advanced cirrhosis patients. This trial mainly aims to evaluate liver histological improvements based on a larger sample. Overall, CVC has a favorable prospect in the application for liver fibrosis.

**Galectin-3 inhibitor**

Galectins are secreted proteins that bind to terminal galactose residues in glycoproteins on components of the ECM. Galectin-3 is highly expressed on Kupffer cells and plays a crucial role in cell adhesion, inflammation, and fibrogenesis. Galectin-3 inhibitor, was safe and well-tolerated in subjects who had a definite histological diagnosis of NASH with advanced fibrosis. FibroScan test showed the potential benefits of GR-MD-02 therapy (8 mg/kg daily) on liver stiffness. Recently, Chalasani et al. conducted a phase II clinical trial of GR-MD-02 in 162 patients with NASH, cirrhosis and portal hypertension. Though improvements of fibrosis or NAFLD activity scores did not differ significantly among groups, a subgroup analysis showed that GR-MD-02 therapy (2 mg/kg biweekly, 52 weeks) did reduce hepatic venous pressure gradient and development of varices in patients without esophageal varices. Spasmodic cough was the only adverse event related to the study drug. A phase III trial has been initiated to evaluate to safety and efficacy of GR-MD-02 in NASH cirrhosis patients without esophageal varices (NCT04365868).

**Pan-caspase inhibitor**

Apoptosis-mediated inflammation and immune response also play a crucial role in the process of fibrosis. Caspases are intracellular cysteine proteases that participate in the process of apoptosis and inflammation through proinflammatory cytokines. Emricasan is a well-tolerated pan-caspase inhibitor. Emricasan (25 mg twice daily, 28 days) can effectively decrease ALT levels, reduce hepatic venous pressure gradient, and improve intrahepatic inflammation in patients with compensated cirrhosis. Most reported adverse events were not serious and the frequent side effect was fatigue. Despite improvements in liver enzymes and hepatic inflammation, it is unlikely that Emricasan exerted an anti-fibrotic effect in 28 days. Although improvements of hepatitis may occur relatively rapidly, attenuation of fibrosis will take longer. A recent phase II trial demonstrated that Emricasan (25 mg twice daily, 3 months) improved liver function and reduced Child-Pugh scores in patients with advanced cirrhosis. Incidence of adverse events was similar between Emricasan and placebo groups. However, it is worth noting that the multiple etiologies of cirrhosis may obscure the actual efficacy when setting clinical scores as endpoints. Optimal doses and long-term efficacy of Emricasan will be explored in an active phase II trial (NCT03205345) in NASH patients with cirrhosis.
ECM and fibrogenesis

**Transforming growth factor-β inhibitor**

Transforming growth factor-β (TGF-β) is considered to be the central factor participating in liver fibrosis. Various strategies have been developed to inhibit the TGF-β pathway. Pirfenidone, an inhibitor of TGF-β, can ameliorate fibrogenesis through inhibiting the activation of HSCs and reducing collagen synthesis in vitro. Borunda et al. found that pirfenidone was well-tolerated and attenuated histological injuries in patients with established advanced cirrhosis after 12 months of treatment. Only 15% of patients developed adverse events, and these included photosensitivity, rash, itching, and nausea. A phase II clinical trial showed that pirfenidone (1200 mg daily, 24 months) improved inflammation, fibrosis, and steatosis in patients with hepatitis C virus-related cirrhosis. All patients on pirfenidone displayed improvements in quality of life and Child-Pugh scores. Side effects such as gastritis and nausea were observed. As viral clearance is indispensable to resolve liver damage, a combination therapy of pirfenidone and antiviral agents may be a new approach for viral fibrosis.

Similarly, based on structural modification of pirfenidone, hydronidone is a novel antifibrotic agent for hepatic fibrosis. An open-label and randomized clinical trial showed that hydronidone was well tolerated and rapidly absorbed in young, healthy volunteers. A phase II clinical trial (NCT02499562) has explored the effective dose and safety of hydronidone capsules in patients with liver fibrosis induced by hepatitis B virus infection in Shanghai General Hospital, Shanghai, China. However, related results have not been posted.

**Lysyl oxidase-like protein 2 antibody**

The lysyl oxidase (LOX) family is crosslinking enzymes overexpressed in liver cirrhosis and contributes to fibrogenesis by catalyzing cross-linkage of collagen and increases the stability of fibrosis in chronic hepatitis settings. Among the five isoforms, LOXL2 is up-regulated by activated HSCs in liver fibrosis. Selective inhibition of LOXL2 suppresses hepatic fibrosis progression and accelerates its reversal in animal fibrosis models.

However, sintuzumab, a humanized monoclonal antibody directed against LOXL2, did not show a promising benefit in clinical trials. In two phase IIb trials, sintuzumab alone (subcutaneous injections: 75 or 125 mg; intravenous infusions: 200 or 700 mg, 96 weeks) was ineffective in decreasing hepatic collagen content or fibrosis stage in patients with bridging fibrosis and hepatitis C virus infection. In another 6-month open-label safety trial, though treatment was well-tolerated, no significant improvements were observed in hepatic venous pressure gradient or liver biopsy after sintuzumab therapy (700 mg, intravenous infusion every 2 weeks for 22 weeks). Also, in patients with PSC, sintuzumab therapy (75 or 125 mg daily, 96 weeks) did not reduce liver collagen content or Ishak fibrosis stage.

**Renin-angiotensin system inhibitor**

The renin-angiotensin system is a crucial regulator of liver fibrosis and portal hypertension. Activated HSCs can secrete angiotensin II that promotes liver fibrosis through angiotensin receptors. Yoshiji et al. demonstrated that angiotensin-converting enzyme inhibitor (ACEI) combination (perindopril: 4 mg daily, 12 months) with interferon decreased serum fibrosis markers (hyaluronic acid, 7S-collagen, P-Ill-P, TGF-β) in patients with chronic refractory hepatitis C. Another clinical trial demonstrated that ACEI (captopril: 25–75 mg daily, 3 months) effectively reduced the portal pressure and prevented variceal bleeding in portal hypertensive patients. The adverse effects of captopril (orthostatic hypotension and dry cough) were not severe enough to stop medication. However, these studies are limited by their lack of histological and immunohistochemical examinations.

Similarly, angiotensin receptor blockades may also attenuate liver fibrosis. Losartan (50 mg daily, 48 weeks) can decrease serum aminotransferase levels and promote histological improvements in NASH with no adverse events. In a randomized open-label controlled study, a combination therapy of candesartan (8 mg daily) and UDCA (600 mg daily) for 6 months also suppressed the expression of fibrosis biomarkers and decreased arterial blood pressure in alcoholic liver fibrosis with no significant complications or side effects. Recently, a phase III trial (NCT03770936) has been posted to compare the efficacy of candesartan and ramipril in hepatitis C virus-related liver fibrosis.

**Challenges**

At present, due to the complex mechanisms involved in hepatic fibrosis, antiepatic fibrosis therapies still face many problems, as outlined here: 1) Hepatic fibrosis has a long disease course. The most reliable method for evaluating the efficacy of treatments is to observe the histopathological changes. In contrast, it is not appropriate to use the clinical serum or radiologic measurements directly as the primary endpoints. 2) Currently, the mechanism involved in liver fibrosis has not been elucidated thoroughly. Murine models may not accurately mimic human liver diseases. 3) Up to now, many antifibrotic trials still assess the efficacy by liver biopsy, which is costly and can be affected by sampling. The invasive inspection may result in complications. 4) Though many clinical trials confirm the efficacy and safety of combination therapy, the role of each component is not defined. 5) Many scholars consider stem cells as a potential option. However, the cellular and molecular basis of liver regeneration in liver fibrosis have not been elucidated totally.

**Conclusions**

Cirrhosis is a severe form of chronic liver disease and is the typical outcome of various etiologies-induced liver injuries. In this article, we reviewed current therapies in clinical trials. Safe and effective therapies may delay the development of decompensated cirrhosis and even reverse fibrosis stage. Apart from conventional cause-specific therapies, the most promising treatments for liver fibrosis are those that target cellular and molecular mechanisms involved in the reversal of fibrosis. As we continue to explore the mechanisms and targets of hepatic fibrosis, effective antifibrotic therapies will be a reality in the future.
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Author contributions
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