Hepatic fibrosis and its regression: the pursuit of treatment

Abstract
Excessive hepatic fibrosis leading towards the cirrhosis is the major determinant of morbidity and mortality in chronic liver disease patients. The reversing hepatic fibrosis has been intensively studied and fuelled up the hope in development of effective and targeted antifibrotic therapy in upcoming years. There are four pillars of pharmacological approach in regression of fibrosis: cessation of damage, the changes in pro-fibrogenic microenvironment, deactivation of activated hepatic stellate cells and degradation of ECM. In this review, we are going to discuss therapeutic concepts and estimate the leading candidate antifibrotic therapy to be introduced in the intervention of hepatic fibrosis.

Keywords: hepatic fibrosis, cirrhosis, fibrosis regression

Abbreviations: HSC, hepatic stellate cell; ECM, extracellular matrix; MMP, matrix metalloproteinases; TIMP, tissue inhibitors of metalloproteinases; TGF-β, transforming growth factor beta; NASH, non-alcoholic steatohepatitis; NKC, natural killer cell; TRAIL, TNF-related apoptosis inducing ligand

Introduction
Hepatic fibrosis is a wound healing response of liver, which is characterized by the deposition of ECM proteins such as collagen during liver injury that maintains organ integrity and protect hepatocytes against various toxic stimuli. Fibrosis becomes problematic when excessive scarring occurs in response to chronic liver injury and progress to end stage hepatic fibrosis - the major determinant of morbidity and mortality in chronic liver disease patients. However, several clinical and experimental mice model studies conclude that liver fibrosis is dynamic bidirectional process but underlying mechanism for resolution of fibrosis yet to be fully understood. The concept of reversing hepatic fibrosis has been intensively studied over the past decade and majorly concern in upcoming years. The reversing hepatic fibrosis has been intensively studied over the past decade and majorly concern in upcoming years. The reversal of fibrosis is critically depend upon - termination of damage source, transformation of fibrogenic microenvironment, deactivation of activated hepatic stellate cells and degradation deposited matrix. Here, we discuss the therapeutic concepts and leading candidates of antifibrotic drugs to be introduced in the intervention of hepatic fibrosis (Figure 1).

There are four pillars of pharmacological approach and their leading candidate antifibrotic drugs prompt fibrosis regression.

a. Cessation of damage source by reducing or controlling tissue injury with pan-caspase inhibitor Emricasan (IDN-6556) that blocks hepatocyte apoptosis, Cathespin-B inhibitor (R-3032) that reduces lip toxicity, Lamivudine, PEG-IFNα and Ribavirin that suppress hepatitis B or C virus replication.

b. Shifting the balance from inflammation to resolution by changing the micro-environmental cue from pro-fibrogenic to anti-fibrogenic with either CCL2-inhibitor mNOX-E36 or dual CCR2/CCR5 inhibitor Cenicriviroc that reduces the infiltration of pro-inflammatory macrophage, FG-3019, a human monoclonal antibody against CTGF that attenuate TGF-β activity.

c. Deactivation or elimination of activated HSC by clearance of fibrogenic HSC with CB2 agonist JWH-133 that promotes apoptosis in activated HSC, CCL5 inhibitor Met-RANTES that attenuate activation of HSC and migration, CCR5 inhibitors maraviroc that inhibits HSC activation, Galectin-3 inhibitors GR-MD-02 and GM-CT-01 which capable to revert severe fibrosis and cirrhosis.

d. Matrix degradation with Lysyl oxidase 2 (LoxL2) specific monoclonal antibody (AB0023) and Simtuzumab (GS-6624, Gilead), prevent Collagen cross-linking.

Cessation of damage source
A number of clinical trials and experimental models observed that control or elimination of primary disease is the most effective antifibrotic treatment. A study from Hepatitis C virus infected patients and in NASH using murine model showed the blockage of hepatocytes apoptosis through administration of Emricasan (IDN-6556), a pan-caspase inhibitor ameliorates liver injury and fibrosis. Similar results were found with Cathespin-B inhibitor R-3032, that attenuate lipotoxicity associated with cholestasis. Anti-viral drug therapy for successful suppression of hepatitis B or C virus replication attenuate progression of fibrosis, and even in reversing advanced fibrosis. Recent, clinical report investigated that the long-term lamivudine therapy improve the histological regression in advanced liver fibrosis/cirrhosis of chronic hepatitis B (AdLF-CHB) patients. The combination therapy of PEG-IFNα and ribavirin in chronic hepatitis C patients significantly decrease fibrosis progression of mild-to-moderate fibrosis (F1/F2/F3).

Change in fibrogenic microenvironment
There is a new insight into the switching of pro-inflammatory to resolution microenvironments that support the recovery of hepatocytes and neighbouring non-parenchymal cells from damage. The modulation of pro-inflammatory cytokine microenvironment and altering immune cells composition encourage the fibrosis regression.
A mice study indicates that transdifferentiation of pro-inflammatory Ly6c\textsuperscript{hi} macrophage into pro-resolution Ly6c\textsuperscript{lo} macrophage accelerated fibrosis resolution.\textsuperscript{10} Pro-resolution macrophages are a rich source of fibrolytic proteases including MMP12 and MMP13 along with MMP9 and TRAIL that promote activated HSC apoptosis.\textsuperscript{3} Leonie Beljaars group have shown the localization macrophages M1 and M2 population in fibrotic septa of human and mice liver. They concluded that M1 macrophages are predominantly present in fibrotic septa during resolution of fibrosis and releases various fibrolytic factors.\textsuperscript{11} RNA-aptamer–based inhibitor of CCL2, termed mNOX-E36 reduces the infiltration of Ly6c\textsuperscript{hi} macrophage in fibrotic mouse models and favouring the shift of intrahepatic macrophage towards pro-resolution Ly6c\textsuperscript{lo} counterparts.\textsuperscript{12} Cenicriviroc, the dual CCR2/CCR5 inhibitor in NASH shows promising results in Phase IIIB clinical trial (NCT02217475) with decreased in inflammation and fibrosis.\textsuperscript{13}

**Deactivation or elimination of activated hepatic stellate cells**

The deactivation or clearance of activated HSC during fibrosis resolution is a goal for therapy involving the process of senescence, apoptosis and inactivation of activated HSC. Senescent HSCs are susceptible for NK cell mediated apoptosis. Gamma delta T cells, Natural Killer T cells and CD8+ cytotoxic T cells also induce apoptosis in activated HSC during fibrosis regression. But more than half of the activated HSC become inactivated and revert to a “quiescent-like” HSC phenotype. These inactivated HSC remain “primed” to fibrogenic stimuli and reactive upon re-exposure.\textsuperscript{14} However, the master switches to push activated HSC towards reversion or death are not known either.

Several studies have been identified various plant extract as an appealing drug candidates to elimination of activated HSCs. Cannabidiol a plant-derived cannabinoid exhibit anti-fibrotic potential preventing proliferation and induces endoplasmic reticulum.
stress mediated apoptosis in activated HSC. It has been reported that endocannabinoid receptors CB2 agonist JWH-133 reduces fibrosis through promoting apoptosis in activated HSC, liver regeneration, regulating pro-inflammatory macrophage polarization and down regulation of the profibrogenic cytokine IL17 by Th17 lymphocytes. Upon liver injury CCL5 chemokine strongly expressed to recruit inflammatory cells and HSC. Inhibition of CCL5 either through Met-RANTES or maraviroc interferes with HSC migration and their activation, and enhances survivability of hepatocytes in mice. Galactin-3 inhibitors GR-MD-02 and GM-CT-01 are also promising candidate in the race of antifibrotic drug in reversing established severe fibrosis and cirrhosis. Recently, Phase-I clinical trial with GR-MD-02 is successfully completed in NASH patients (NCT01899859).

Matrix degradation

Degradation of the excessive extracellular matrix is the crucial step for the resolution of fibrosis. Reversibility of fibrosis is associated with reduced TIMP expression with enhanced MMPs expression that degrade ECM components such as collagen. During fibrosis resolution pro-resolution macrophage releases MMP9, MMP12 and MMP13 fibrolytic proteases along with TRAIL that promote the Clarence of activated HSC. A mice study showed that the administration of TIMP-1 antibody attenuated liver fibrosis with decreased HSC activation. Collagen cross-linking enzyme Lysyl oxidase 2, the specific monoclonal antibody and non-competitive allosteric antibody Simtuzumab (GS-6624, Gilead), a suppressor of HSC migration and their activation, and enhances survivability of lymphocytes.

Conclusion

Recent clinical trials and understanding of cellular and molecular mechanisms of liver fibrosis regression encouraged the hope in development of effective and targeted anti-fibrotic therapy. Combinational therapeutics can be hold most promises in fibrosis regression, but it requires extensive basic and clinical research to introduce effective and safe, anti-fibrotic therapies in near future.

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Conflict of interest

Author declares that there is no conflict of interest.

References


