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 cirrhosis - 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 underling 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 regression of fibrosis is critically depend upon - termination of damage source, transformation of fibrogenic microenvironment, deactivation or elimination of activated HSC 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-IFN α 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-E3 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 Cathepsin-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-IFN α 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}

![Concept of Hepatic Fibrosis Regression](image)

**Figure 1** Concept of hepatic fibrosis regression.

Pharmacological targeting of TGF-β, a most potent pro-fibrogenic cytokine established successful approach in treatment of experimental fibrogenesis but exert adverse effect in human.\textsuperscript{14} FG-3019, a human monoclonal antibody against CTGF, co-factor require for TGF-β activity prevent and reverse the process of fibrosis in mice model and currently in clinical trial.\textsuperscript{15} Other cells also participate in hepatic fibrosis regression such as dendritic cells that express fibrolytic MMP-9 that favour matrix degradation and NKC that induces apoptosis of activated and senescent myofibroblast via NKG2D and TRAIL, respectively.\textsuperscript{16,17}

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

The deactivation or clearance of activated HSC during fibrosis regression is a goal for therapy involving the process of senescence, apoptosis and inactivation of activated HSC. Senescence 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{18} 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...
Hepatic fibrosis and its regression: the pursuit of treatment

Hepatic fibrosis and its regression: the pursuit of treatment

24, 25, 3

Áñez J. New determinants of prognosis in bacterial infections in cirrhosis. J Clin Invest. 2003;112(2):152–159.

6. 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(2):324–329.

7. Canbay A, Guicciardi ME, Higuchi H, et al. Cathespin B inactivation attenuates hepatic injury and fibrosis during cholestasis. J Clin Invest. 2012;120(6):2316–2327.

8. Xu B, Lin L, Xu G, et al. Long-term lamivudine treatment achieves regression of advanced liver fibrosis/cirrhosis in patients with chronic hepatitis B. J Gastroenterol Hepatol. 2015;30(2):372–378.

9. Vukanov-Bijedic Z, Husic-Selimovic A, Mehinovic L, et al. Analysis of Effect of Antiviral Therapy on Regression of Liver Fibrosis in Patient with HCV Infection. Mater Sociomed. 2014;26(3):172–176.

10. Ramachandran P, Pellicoro A, Vernon MA, et al. Differential Ly-6C expression identifies the recruited macrophage phenotype, which orchestrates the resolution of murine liver fibrosis. Proc Natl Acad Sci. 2012;109(46):E3186–E3195.

11. Beljaars L, Schippers M, Reker-Smit C, et al. Hepatic Localization of Macrophage Phenotypes during Fibrogenesis and Resolution of Fibrosis in Mice and Humans. Front Immunol. 2014;5:430.

12. Baeck C, Wei X, Bartneck M, et al. Pharmacological inhibition of the chemokine C-C motif chemokine ligand 2 (monocyte chemoattractant protein 1) accelerates liver fibrosis regression by suppressing Ly-6C(+) macrophage infiltration in mice. Hepatology.2014;59(3):1060–1072.

13. Friedman S, Sanyal A, Goodman Z, et al. Efficacy and safety study of cenicriviroc for the treatment of non-alcoholic steatohepatitis in adult subjects with liver fibrosis: CENTAUR Phase 2b study design. Contemp Clin Trials. 2016;47:356–365.

14. Dooley S, ten Dijke P. TGF-β in progression of liver disease. Cell Tissue Res. 2012;347(1):245–256.

15. Lipson KE, Wong C, Teng Y, et al. CTGF is a central mediator of tissue remodeling and fibrosis and its inhibition can reverse the process of fibrosis. Fibrogenesis & Tissue Repair. 2012;5(Suppl 1):S24.

16. Jiao J, Sastre D, Fiel MI, et al. Dendritic cell regulation of carbon tetrachloride-induced murine liver fibrosis regression. Hepatology. 2012;55(1):244–255.

17. Tian Z, Chen Y, Gao B. Natural killer cells in liver disease. J Hepatol. 2013;57(4):1654–1662.

18. Lee YA, Wallace MC, Friedman SL. Pathobiology of liver fibrosis: a translational success story. Gut. 2015;64(5):830–841.

19. Lim MP, Devi LA, Rozenfeld R. Cannabinoid causes hepatic stellate cell death through a mechanism of endoplasmic reticulum stress-induced apoptosis. Cell Death Dis. 2011;2:e170.

20. Guillot A, Hamdaoui N, Bizy A, et al. Cannabinoid receptor 2 counteracts interleukin-17-induced immune and fibrogenic responses in mouse liver. Hepatology. 2014;59(1):296–306.

21. Baeck C, Wei X, Bartneck M, et al. Pharmacological inhibition of the chemokine C-C motif chemokine ligand 2 (monocyte chemoattractant protein 1) accelerates liver fibrosis regression by suppressing Ly-6C(+) macrophage infiltration in mice. Hepatology.2014;59(3):1060–1072.

22. Muñoz-Luque J, Ros J, Fernández-Varo G, et al. Regression of fibrosis after chronic stimulation of cannabinoid CB2 receptor in cirrhotic rats. J Pharmacol Exp Ther. 2008;324(2):475–483.

23. Teixeira-Clerc F, Belot MP, Manin S, et al. Beneficial paracrine effects of cannabinoid receptor 2 on liver injury and regeneration. Hepatology. 2010;52(3):1066–1059.

24. Berres ML, Koenen RR, Rueland A, et al. Antagonism of the chemokine CCL5 ameliorates experimental liver fibrosis in mice. J Clin Invest. 2010;120(11):4129–4140.

References

1. Bourbonnais E, Raymond VA, Ethier C, et al. Liver Fibrosis Protects Mice from Acute Hepatocellular Injury. Gastroenterology. 2012;142(1):130–139.

2. Acevedo J, Fernández J. New determinants of prognosis in bacterial infections in cirrhosis. World J Gastroenterol. 2014;20(23):7252–7259.

3. Pellicoro A, Ramachandran P, Iredale JP, et al. Liver fibrosis and repair: immune regulation of wound healing in a solid organ. Nat Rev Immunol. 2014;14(3):181–194.

4. Frank Tacke, Christian Trautwein. Mechanisms of liver fibrosis resolution. Journal of Hepatology. 2015;63(4):1038–1039.

5. 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(3):953–966.

Citation: Biswas S, Sharma S. Hepatic fibrosis and its regression: the pursuit of treatment. J Liver Res Disord Ther. 2016;2(2):36-39.

DOI: 10.15406/jldt.2016.02.00021
25. Ochoa-Callejero L, Pérez-Martínez L, Rubio-Mediavilla S, et al. Maraviroc, a CCR5 Antagonist, Prevents Development of Hepatocellular Carcinoma in a Mouse Model. *PLoS One*. 2013;8(1):e53992.

26. Traber PG, Chou H, Zomer E, et al. Regression of fibrosis and reversal of cirrhosis in rats by galectin inhibitors in thioacetamide-induced liver disease. *PLoS One*. 2013;8(10):e75361.

27. Musso G, Cassader M, Gambino R. Non-alcoholic steatohepatitis: emerging molecular targets and therapeutic strategies. *Nat Rev Drug Discov*. 2016;15(4):249–274.

28. Xu R, Zhang Z, Wang FS. Liver fibrosis: mechanisms of immune-mediated liver injury. *Cellular & Molecular Immunology*. 2012;9:296–301.

29. Parsons CJ, Bradford BU, Pan CQ, et al. Antifibrotic effects of a tissue inhibitor of metalloproteinase-1 antibody on established liver fibrosis in rats. *Hepatology*. 2004;40(5):1106–1115.

30. Barry-Hamilton V, Spangler R, Marshall D, et al. Allosteric inhibition of lysyl oxidase-like-2 impedes the development of a pathologic microenvironment. *Nat Med*. 2010;16(9):1009–1017.

31. Su TH, Kao JH, Liu CJ. Molecular Mechanism and Treatment of Viral Hepatitis-Related Liver Fibrosis. *Int J Mol Sci*. 2014;15(6):10578–10604.