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Anti-fibrotic Therapy for Chronic Liver Diseases Review

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Abstract – Liver fibrosis reflects tissue scarring in the liver because of the accumulation of over the top extracellular matrix in light of constantly persistent liver injury. Hepatocyte cell death can trigger capillarization of liver sinusoidal endothelial cells, stimulation of immune cells including macrophages and Kupffer cells, and initiation of hepatic stellate cells (HSCs), bringing about progression of liver fibrosis. Liver cirrhosis is the terminal condition of liver fibrosis and is related with serious complications, like liver failure, portal hypertension, and liver malignant growth. In any case, compelling treatment for cirrhosis has not yet been set up, and liver transplantation is the main revolutionary treatment for severe cases. Studies examining HSC activation and guideline of collagen creation in the liver have made leap forwards in ongoing many years that have advanced the information with respect to liver fibrosis pathophysiology. In this review, we sum up molecular mechanisms of liver fibrosis and discuss the improvement of novel anti- fibrotic treatments.

Keywords – Fibrosis; Hepaticstellatecells; Myofibroblasts; Extracellular matrix; Drug therapy.

INTRODUCTION

Liver cirrhosis is a late-phase of chronic hepatitis and presently the 11th most common reason for death worldwide [1]. Decompensated cirrhosis, the most advanced phase of cirrhosis, is joined by severe complications, including liver failure, opportunistic infections, and portal hypertension (bringing about ascites, hepatic encephalopathy, or gastroesophageal varices), that compromise the existences of patients [2]. Cirrhosis is accompanied by extensive tissue scarring and an increment in intrahepatic vascular resistance. Cirrhosis developed from chronic hepatitis, that can be brought about by hepatitis B infection (HBV), hepatitis C infection (HCV), alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH), autoimmune hepatitis, and genetic diseases, including hemochromatosis and Wilson's infection [3]. Recently, progress made in antiviral medications has added to a decline in viral hepatitis, while the extent of cirrhosis and liver disease brought about by ALD and NASH has been increasing, especially in western countries [4]. Studies on liver fibrosis, including the development of cirrhosis treatment, has gained amazing progress. Nonetheless, successful medications for cirrhosis treatment are not yet accessible for clinical use. Advancement of effective cirrhosis treatments requires the capacity to target explicit cell types, yet additionally to explain further systems of liver fibrosis with a far reaching comprehension of intercellular molecular networks. This review will feature the current status of anti-fibrotic drug advancement and review the recent studies researching the molecular mechanisms of liver fibrosis.

I. CELL-TARGETING STRATEGY FOR ANTI-FIBROTIC DRUGS

Liver fibrosis is the most widely pathology of cirrhosis and is portrayed by progressive accumulation of extracellular matrix (ECM), which destroys the lobule architecture of the liver [5]. Most of the liver injury is related with hepatocyte damage. Liver injury prompts the accelerated production of ECM parts, like collagens, elastin, and proteoglycans [6]. This bio adaptive response

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shields hepatocytes from cell death and adds to liver recovery. Notwithstanding, constant liver injury increases activated hepatic stellate cells (HSCs) that produce excessive ECM components, basically type 1 collagen encoded by the COL1A1 and COL1A2 genes [7]. Since the amount of type I collagen in liver tissues results from the balance between type 1 collagen production and the activities of framework metalloproteinase (MMPs) and tissue inhibitor of MMPs, interruption of the balance can prompt progression of liver fibrosis [8,9]. Furthermore, upon liver injury, bone marrow-derived inflammatory cells, including macrophages, accelerate HSC inactivation with high production of type I collagen. Consequently, systems for liver fibrosis treatment include: 1) inhibition of HSC activation; 2) decrease of fibrotic scar development; 3) immune modulation and 4) protection from hepatocyte.

Current therapeutic techniques for liver fibrosis depend basically on the elimination of aetiologies. Clinical proof for liver fibrosis resolution has risen up out of studies researching antiviral treatments for viral hepatitis [10-12], life style changes, and bariatric surgery for metabolic liver disease [13], recommending that liver fibrosis is without a doubt reversible. Table 1 outlines a part of the liver fibrosis clinical preliminaries that are presently dynamic or in enlisting phase 1–3. Here, developing anti- fibrotic drugs are summed up according to the viewpoint of cell-focusing on strategies.

Current active or recruiting phase 1–3 clinical trials for liver fibrosis (ClinicalTrials.gov)

Trial number	Drug	Disease	Phase	Study type
NCT03809052	GB1211	NASH	Phase 1	Safety
NCT03912532	NGM282	NASH	Phase 2	Efficacy, safety
NCT03486899	BMS-986036	NAFLD/NASH	Phase 2	Efficacy, safety
NCT03486912	BMS-986036	NAFLD/NASH	Phase 2	Efficacy
NCT03205345	Emricasan	NASH	Phase 2	Efficacy, safety
NCT03656068	Nitazoxanide	NASH	Phase 2	Efficacy, safety
NCT04099407	Pirfenidone	CLD	Phase 2	Efficacy, safety
NCT03517540	Tropifexor and cenicriviroc	NASH	Phase 2	Efficacy, safety
NCT04173065	VK2809	NASH	Phase 2	Efficacy
NCT04104321	Aramchol	NASH	Phase 3	Efficacy, safety
NCT03028740	Cenicriviroc	NASH	Phase 3	Efficacy, safety
NCT02704403	Elafibranor	NASH	Phase 3	Efficacy, safety
NCT03900429	MGL-3196	NASH	Phase 3	Efficacy, safety
NCT02548351	Obeticholic Acid	NASH	Phase 3	Efficacy, safety

NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; CLD, chronic liver disease.

1-1 Inhibition of HSC activation

HSCs have a quiescent state in healthy liver tissue. Quiescent HSCs (qHSCs) keep retinol as retinyl palmitate in lipid droplets. Because of liver injury, HSCs initiate and transdifferentiate into myofibroblast-like cells [7,14]. Activated HSCs, characterized by diminished lipid drops and improved expression of α-smooth muscle actin, have a proliferative phenotype and produce excessive ECM parts, essentially collagens, bringing about progression of liver fibrosis [15,16]. HSCs are activated by cytokines, like

interleukins (ILs), tumour necrosis factor-alpha (TNF-α), transforming growth factor-β (TGF-β), platelet-derived growth factor, and chemokines, for example, monocyte chemo -attractant protein-1 (otherwise called C-C motif ligand 2 [CCL2]), and C-X-C motif ligand 9. Hepatocyte cell death brought about by ongoing liver injury causes inflammatory activity of liver immune cells, predominantly macrophages, prompting an increment in these secretory factors [17]. Likewise, pathogen associated molecular pattern (PAMPs, for example, lipopolysaccharides released from organisms, DNA, and damaged associated molecular pattern(DAMPs) got from injured hepatocytes, can initiate HSCs. PAMPs and DAMPs bind to pattern recognition receptors, for example, toll-like receptor 4, which then, at that point, improves the nuclear translocation of nuclear factor-kappa B (NF-κB) by means of myeloid differentiation primary response 88 (MyD88), and downregulates expression of BMP and activin membrane bound inhibitor, accordingly limiting TGF-β signalling [18,19].

Peroxisome proliferator-initiated receptors (PPARs) are ligand-enacted transcription factors of the nuclear hormone receptor superfamily that assume major regulatory roles in energy homeostasis and metabolic function. Among the three isoforms of PPARs (PPARα, PPARγ, and PPARβ/δ), PPARγ is particularly considered as a promising therapeutic target of liver fibrosis. The expression of PPARγ diminishes HSC activation, however it is profoundly communicated in quiescent HSCs [20]. A randomized phase 3 clinical preliminary of pioglitazone, a synthetic insulin sensitizing PPARγ agonist, announced improved steatosis and lobular inflammation without a critical impact on fibrosis, in non-cirrhotic NASH patients [21]. Notwithstanding, meta-investigation of eight randomized clinical preliminaries for thiazolidinedione treatment showed that pioglitazone treatment, for as long as two years, was related with fibrosis improvement at any stage and NASH resolution [22]. In addition, elafibranor is a dual PPARα/δ agonist that has shown liver protective impacts for steatosis, inflammation, and fibrosis in murine models of non-alcoholic greasy liver disease (NAFLD)/NASH and liver fibrosis [23]. Results from a post-hoc analysis from a phase 2 preliminary (NCT01694849) for elafibranor treatment (120 mg/day for 1 year) propose that it resolved NASH without worsening fibrosis in patients with moderate to severe NASH [24]. Further, a phase 3 preliminary (NCT02704403) is in progress in NASH patients without cirrhosis, with an endpoint characterized as resolution of NASH without deteriorating of fibrosis. Notwithstanding, as per an interim analysis of this preliminary, elafibranor showed no significant impact on NASH resolution without worsening of fibrosis [25].

Foresaid X receptor (FXR), which binds to bile acids as ligands, upgrades insulin sensitivity and fatty acid beta-oxidation, while diminishing gluconeogenesis and lipogenesis in hepatocytes [26]. FXR is exceptionally expressed in the small digestive tract and liver and is likewise expressed in HSCs. Curiously, overexpression of FXR inhibited production of collagen in HSCs [27].

In the meantime, obeticholic acid(OCA), a semisynthetic subordinate of cheno deoxy cholic acid, is the particular FXR agonist. In a phase 2 preliminary, organization of 25 or 50 mg of OCA for 6 weeks expanded insulin sensitivity, and decreased markers of liver inflammation and fibrosis in patients with type 2 diabetes mellitus and NAFLD (NCT00501592) [28]. Besides, an interim analysis of a continuous phase 3 study in patients with NASH (NCT02548351) recently detailed that daily administration of 25 mg of OCA significantly improved fibrosis by something like one phase without worsening NASH [29]. However, this report has recommended that NASH patients with non-cirrhotic advanced fibrosis may benefit from OCA treatment, the U.S. Food and Drug Administration (FDA) has not supported OCA for the treatment of NASH fibrosis and has requested the submission of extra post-interim analysis on the efficacy and safety of the ongoing study [30].

Wnt/β-catenin signalling is related with the development of tissue fibrosis, including liver fibrosis [31]. PRI-724, a cyclic AMP-response element binding protein (CBP)/β-catenin inhibitor, has been displayed to inhibit HSC activation and collagen production in HCV transgenic mice [32]. Furthermore, inhibition of CBP/β-catenin signalling reported lessened liver fibrosis through diminished hepatocyte apoptosis and suppression of collagen-delivering cell activation. As indicated by a phase 1 study, intravenous administration of 10 or 40 mg/m2/day of PRI-724 more than 12 weeks was very much tolerated by patients with HCV cirrhosis showing dose dependant histological improvement (>2 points decline in histologic activity index score) in 3/12 patients, and deterioration by 2 points in 2/12 patients [33]. A phase1/2a clinical preliminary for PRI-724 in patients with hepatitis B or C related liver cirrhosis is ongoing.

Oxidative stress is a known reason for liver fibrosis progression, especially in NASH [34]. NADPH oxidase (NOX) is a common source of reactive oxygen species (ROS) [35,36], and NOX1, 2, and 4 assume significant parts in the activation of HSCs [37,38]. GKT137831, a NOX1/4 inhibitor, supresses ROS production, NOX, and fibrotic gene expression, while attenuating liver fibrosis in carbon tetrachloride (CCl4)- induced liver fibrosis in mice [39]. A phase 2 clinical preliminary for GKT137831 in patients with primary biliary cholangitis (PBC) (NCT03226067) has been finished and results are awaiting publication.

Nitazoxanide (NTZ), an antiprotozoal agent, is the main FDA-supported medication for Cryptosporidium infection [40]. Recently, NTZ was distinguished as a potent anti- fibrotic agent by a phenotypic screening approach pointed toward finding a compound capable for interfering with HSC activation. NTZ was found to diminish liver fibrosis in murine models of both CCl4-induced liver fibrosis and diet-induced NASH [41]. Furthermore, NTZ, along with elafibranor, work synergistically to diminish liver fibrosis in a murine NASH model [42]. A phase 2 preliminary to assess the viability of NTZ in NASH patients with severe fibrosis is progressing.

Cytoglobin (CYGB), the fourth human globin, found in our research facility, is most abundantly expressed in HSCs among liver cells [43,44]. CYGB can bind with oxygen and nitric oxide, and is accepted to shield HSCs from ROS [45]. TGF-β1-induced suppression of human CYGB expression is accounted for to contribute to the promotion of HSC activation through loss of cell tolerance to exogenous oxidative stress and oxidative DNA damage in HSCs, bringing about accelerating of liver fibrosis [46]. Cygb-insufficient mice gave progressed liver fibrosis and susceptibility to liver malignant growth progression in diethyl nitrosamine-incited hepatocellular carcinoma and NASH models [47]. Besides, in a rodent model, CCl_4-induced liver fibrosis was reduced by administration of recombinant human CYGB protein [48]. Fibroblast growth factor 2, which enhances CYGB expression, attenuated the progression of liver fibrosis in mice with bile channel ligation [49]. CYGB protein may, hence, address a potential anti- fibrotic drug.

Removal of activated HSCs offers an alternative possible therapeutic strategy for liver fibrosis. Terminal deoxynucleotidyl transferase dUTP nick end labelling positive HSCs are supposedly expanded after decreased liver fibrosis during the recovery process from bile duct ligation-induced liver injury in rodents [50]. Additionally, human and rat liver myofibroblasts experience constitutive NF-κB activation, which advances survival by initiating expression of anti- apoptotic genes, for example, growth arrest and DNA-damage inducible 45 beta and B-cell lymphoma 2 [51]. In this way, studies on the effectiveness of targeted HSC apoptosis as a therapeutic strategy for liver fibrosis are as a rule effectively conducted [52,53].

1-2 Decrease of fibrotic scar development

Lysyl oxidase-like 2 (LOXL2) is a copper-dependant amine oxidase secreted by HSCs that contributes to liver fibrosis by catalysing collagen cross-linking [54,55]. In murine models of fibrosis, inhibition of LOXL2 by an anti- LOXL2 murine monoclonal antibody diminished liver fibrosis and expanded survival [54].

In the meantime, simtuzumab, a humanized monoclonal antibody against LOXL2, inhibits the enzymatic activity of LOXL2 [56]. Unfortunately, in two phase 2b preliminaries for NASH patients with bridging fibrosis or compensated cirrhosis (NCT01672866 and NCT01672879), simtuzumab failed to diminish hepatic collagen content or hepatic venous pressure gradient (HVPG), respectively [57]. Additionally, in a phase 2 study on primary sclerosing cholangitis patients (NCT01672853), treatment with simtuzumab for a considerable length of time didn't diminish fibrosis stage, progression to cirrhosis, or frequency of clinical events [58].

Collagen 1 accounts for the most plentiful collagen in fibrotic livers [59]. A past study showed that lipid nanoparticles loaded with small interfering RNA (siRNA) against the procollagen α1(I) gene specifically diminished complete hepatic collagen content in murine model of liver fibrosis [60]. Besides, one more study utilizing transgenic mice with inducible collagen 1 knockdown announced a 40–50% decrease in hepatic collagen accumulation with extra anti-inflammatory effects [61]

Heat shock protein 47 (HSP47) is a collagen-specific molecular chaperone fundamental for procollagen folding in the endoplasmic reticulum [62,63]. Sato et al. [64] detailed that vitamin A-coupled liposomes conveying siRNA against mRNA encoding rodent gp46, a homolog of HSP47, resolved liver fibrosis in a rodent model of liver fibrosis. The efficacy of BMS-986263, a HSP47 siRNA conveying lipid nanoparticle, has been explored in patients with F3–4 liver fibrosis (NCT02227459); the interim results for which have shown that BMS-986263 was well endured and showed histologic improvement in fibrosis [65].

1-3 Immune modulation

Infiltrating inflammatory cells, and macrophages, are engaged with liver fibrosis. PAMPs and DAMPs can stimulate the activation of Kupffer cells, resident macrophages in the liver, and inflammatory reactions in the liver. Activated Kupffer cells promote HSC activation, yet in addition secrete chemokines, including C-C chemokine ligand (CCL) types 2 and 5 (CCL2 and CCL5), which along with their separate receptors, C-C chemokine receptor (CCR) types 2 and 5 (CCR2 and CCR5), contribute to liver fibrosis and inflammation [66-70]. In response to liver injury, Kupffer cells secrete CCL2 and elevate monocyte enlistment to the liver,

trailed by their development into supportive of provocative LY6Chigh macrophages [71,72].pro-inflammatory cytokines secreted from the macrophages activate HSCs by stimulating collagen production [73]. CCR2/CCR5 inhibitor, and cenicriviroc (CVC) reportedly decreased recruitment of pro-inflammatory macrophages and applied anti- fibrotic impacts in animal models of liver fibrosis [74,75].

Also, a phase 2b randomized study (NCT02217475) has revealed that after 1 year of CVC treatment, twice as many subjects accomplished an improvement in fibrosis without worsening of steatohepatitis, compared with placebo group [76]. A rollover study on utilizing CVC for the treatment of liver fibrosis in NASH patients is ongoing (NCT03059446). Currently, one more rollover study to evaluate the long term safety of CVC is being conducted in patients with NASH who have contributed in either the CENTAUR study (NCT02217475) or the AURORA study (NCT03028740). Also, a combination treatment including CVC and tropifexor (a FXR agonist), is under investigation and has reported improved inflammation and ballooning in an animal model of NASH. A stage 2 preliminary of this combination therapy in patients with NASH and liver fibrosis (F2 or 3) is ongoing [77].

Galectin-3 is primarily secreted by activated macrophages and is engaged with the pathophysiology of liver fibrosis [78-80]. Previous studies have shown that belapectin (otherwise called GRMD-02), an inhibitor or galectin-3, showed potent anti- fibrotic efficacy in mouse and rats models of liver fibrosis [81,82]. While a phase 2b investigation of belapectin (NCT02462967) didn't evoke significant effects for fibrosis following treatment for quite a long time in patients with NASH, cirrhosis, and entrance hypertension, 2 mg/kg of belapectin viably diminished HVPG and development of varices in a subgroup analysis of patients without oesophageal varices [83]. A phase 2b/3 clinical study in patients with NASH cirrhosis without varices is ongoing (NCT04365868). Furthermore, GB1211, another galectin-3 receptor inhibitor, is being researched for its safety and tolerability in a stage 1study (NCT03809052).

Also, inflammasomes in hepatic macrophages are significant players in liver fibrosis. A well-studied PRR, NLR family pyrin domain containing 3 (NLRP3), forms a complex referred to as the "NLRP3 inflammasome," which produces and secretes inflammatory cytokines [84-86]. Calvente et al. [87] exhibited that neutrophil derived microRNA-223 acts as a silencer of Nlrp3 in hepatic macrophages, coming about in attenuated fibro genesis through inhibition of collagen synthesis in HSCs. Accordingly, macrophage-specific inhibition of inflammasomes might be a promising strategy for liver fibrosis therapeutics.

1-4 Protection from hepatocyte death

Preventing hepatocyte death by eliminating of the cause for hepatocyte injury is perhaps the most essential treatment strategy for liver fibrosis. Recently, many new medications to prevent hepatocyte death have been developed and tried, especially for NASH. Anti-fibrotic drugs focusing on hepatocyte injury and death brought about by NASH or different variables, are summed up.

1-5 NASH

Previous reports have shown that hepatocyte cell death prompts liver inflammation and HSC activation, prompting liver fibrosis progression; thus, inhibition of hepatocyte death could diminish HSC activation in animal models [88,89]. Recently, randomized placebo treatment controlled preliminaries for emricasan, a pan- caspase inhibitor, explored its efficacy in NASH patients. However, emricasan somewhat further improved HVPG in cirrhotic NASH patients (NCT02960204) [90], it didn't work on liver inflammation or fibrosis, but instead tended to worsen hepatocyte ballooning in patients with NASH associated F1–F3 fibrosis (NCT02686762) [91]. Besides, emricasan didn't meet the primary endpoint in a stage 2b preliminary in patients with decompensated NASH cirrhosis (NCT03205345) [92].

Apoptosis signal-managing kinase 1 (ASK1) is activated by different pathological stimuli, including intracellular oxidative stress and endoplasmic reticulum stress. Activation of ASK1 is engaged with hepatocyte apoptosis and necrosis, leading to inflammation and fibrosis in the liver [93-95]. A specific ASK1 inhibitor, selonsertib, was examined for NASH treatment in a stage 2 clinical preliminary, and showed worked on histological fibrosis in NASH patients with F2–3 fibrosis following 24 weeks of treatment [96]. Nonetheless, randomized phase 3 preliminaries in NASH patients with F3 (NCT03053050) and F4 fibrosis (NCT03053063) detailed no significant anti- fibrotic impact following 48 weeks of selonsertib monotherapy [97].

TNF-α likewise initiates hepatocyte death and acute liver failure [98,99]. Apoptotic bodies produced during hepatocyte death are engulfed by Kupffer cells, bringing about improved production of death ligands (TNF-α, TRAIL, and FasL) by Kupffer cells and further induction of hepatocyte death [100-102]. Pirfenidone (PFD), an orally bioavailable pyridine derivative, is approved for the treatment of idiopathic pulmonary fibrosis [103,104]. A previous study has announced that therapy with PFD for 24months worked

on hepatic inflammation and fibrosis in patients with ongoing hepatitis C [105]. Nonetheless, the mechanism of action of PFD has not been completely explained. A recent study announced that PFD attenuated liver fibrosis in western fed melanocortin 4 receptor-deficient mice (NASH model mice). PFD likewise prevented TNF-α-induced hepatocyte apoptosis with diminished activation of caspase-8 and caspase-3, recommending that PFD applies anti- fibrotic impacts in NASH by means of inhibiting of hepatocyte death [106]. A phase 2 study (NCT04099407) assessing the anti-fibrotic impact and safety of PFD therapy for 12 months in patients with persistent liver infections has as of late announced a significant decrease of fibrosis in 35% of PFD-treated patients [107].

BMS-986036 (Pegbelfermin) is a polyethylene glycol-formed recombinant analog of human fibroblast development factor 21 [108,109], which is a hepatokine that manages glucose and lipid metabolism in white adipose tissue [110]. As indicated by the aftereffects of a phase 2 study in NASH patients (NCT02413372), pegbelfermin administration for 16weeks (10 mg daily, or 20 mg once per week) altogether diminished both hepatic fat fraction, as estimated by attractive reverberation imaging-proton thickness fat fraction, and mean liver stiffness, as estimated by magnetic resonance elastography, compared with the placebo treatment group [111]. Phase 2 preliminaries researching the histologic impacts of pegbelfermin are continuous in NASH patients with bridging fibrosis (NCT03486899), just as in those with NASH and compensated cirrhosis (NCT03486912).

Statins which repress the activity of hydroxymethylglutaryl-coenzyme A reductase, are applied worldwide as lipid-lowering agents for dyslipidaemia. Previous studies have revealed that statins apply anti-inflammatory and anti- fibrotic impacts in animal models of chronic liver disease [112]. Albeit two ongoing studies, based on retrospective cohort studies, have proposed that statins might be useful in diminishing steatosis and fibrosis, just as for inhibiting disease progression in patients with NAFLD [113,114], forthcoming studies are expected to affirm their effects.

Aramchol is an inhibitor of stearoyl-coenzyme A desaturase 1 (SCD1), which converts unsaturated fats to monounsaturated fatty acids. Inhibition of SCD1 diminishes unsaturated fatty acids synthesis, which thus lessens liver fat with further improved insulin resistance [115]. In a phase 2 preliminary (NCT01094158), administration of aramchol for 3 months significantly diminished liver fat substance in NAFLD patients [116]. In the meantime, a phase 3 preliminary assessing the efficacy of aramchol in NASH patients with fibrosis, is progressing.

Thyroid chemical receptor beta (THR-β), which is profoundly communicated in hepatocytes, directs lipid metabolism in the liver [117]. VK2809 and resmetirom (MGL-3196) are THR-β agonists that can activate lipid metabolism prompting enhancements in NASH [118]. Phase 2 preliminaries for these medications have revealed a decrease in liver fat and low-density lipoprotein cholesterol [119,120]. Also, VK2809 is being explored for its efficacy and safety in a phase 2b preliminary for NASH patients (NCT04173065), while resmetirom is being evaluated in a phase 3 preliminary for NASH patients with F2–3 fibrosis (NCT03900429).

FGF19 is a hormone engaged with the regulation of bile acid metabolism [121]. Previous studies have announced decreased concentrations of circulating FGF19 and raised bile acid focus in NAFLD patients [122,123] recommending that FGF19 dysregulation may be engaged with NASH progression. NGM282, a FGF19 simple, represses bile acid synthesis without FGF19-related hepatocarcinogenesis [124,125]. In mouse models of NASH, NGM282 applies anti-steatotic, anti-inflammatory, and anti-fibrotic impacts without promoting liver tumorigenesis [126]. A new phase 2 preliminary (NCT02443116) has exhibited that NGM282 lessens liver fat content, as well as markers of liver inflammation and fibrosis in NASH patients [127].

II. Alternative Causes Of Liver Fibrosis

The advancement of antiviral agents against HBV and HCV is the best technique to prevent liver fibrosis progression. In a preliminary incorporating 348 patients with ongoing hepatitis B, antiviral treatment with tenofovir brought about relapse of liver fibrosis in 51% of the members, incorporating patients with cirrhosis [10]. Different reports have shown that drawn out viral suppression with entecavir lead to histologic improvement of liver fibrosis [11,128,129]. Essentially, supported virologic reaction (SVR) by antiviral treatment for chronic HCV disease is additionally associated with liver fibrosis regression. A study detailed that 50–60% of cirrhosis patients who accomplished SVR by interferon treatment experienced histological relapse of liver fibrosis [12,130]. Patients who accomplished SVR following treatment with direct-acting antiviral agents additionally experienced liver fibrosis regression [131,132].

Corticosteroids and immunosuppressive agents are the primary drugs used to treat autoimmune hepatitis. Corticosteroids have been displayed to work on liver fibrosis in 66% of patients with autoimmune hepatitis [133]. In the interim, immunosuppressive

treatments are not effective for PBC. In any case, ursodeoxycholic corrosive, the fundamental medication for PBC, apparently postpones the progression of liver fibrosis in patients with early stage PBC [134].

III. Conclusion

Liver fibrosis, including cirrhosis, is accepted to be potentially reversible. Hence, it is fundamental to work on liver fibrosis to treat the underlying liver problem. Many anti- fibrotic drugs focusing on hepatocytes, HSCs, and immune cells are being explored in clinical preliminaries. Notwithstanding, the results of many of these preliminaries recommend that treatment with a single agent isn't adequate to ameliorate advanced liver fibrosis. Subsequently, combination treatments involving drugs that follow up on different mechanisms ought to be additionally researched, alongside the development of anti- fibrotic drugs with novel mechanisms. In near future, therapeutic agents for liver cirrhosis will progress toward clinical application, taking advantage of the reversibility of liver fibrosis as a primary strategy.

Abbreviations

ALD: alcoholic liver disease

ASK1: apoptosis signal-regulating kinase 1

CBP: cyclic AMP-response element binding protein-binding protein

CCL: C-C chemokine ligand

CCL2: C-C motif ligand

CCl_4: carbon tetrachloride

CCR: C-C chemokine receptor

CVC: cenicriviroc

CYGB: cytoglobin

DAMPs: damaged-associated molecular patterns

ECM: extracellular matrix

FDA: Food and Drug Administration

FXR: farnesoid X receptor

HBV: hepatitis B virus

HCV: hepatitis C virus

HSCs: hepatic stellate cells

HSP47: heat shock protein 47

HVPG: hepatic venous pressure gradient

ILs: interleukins

LOXL2: lysyl oxidase-like 2

MMPs: matrix metalloproteinases

NAFLD: non-alcoholic fatty liver disease

NASH: non-alcoholic steatohepatitis

NF-κB: nuclear factor-kappa B

NLRP3: NLR family pyrin domain containing 3

NOX: NADPH oxidase

NTZ: nitazoxanide

OCA: obeticholic acid

PAMPs: pathogen-associated molecular patterns

PBC: primary biliary cholangitis

PFD: pirfenidone

Post-hoc analysis: In a scientific study, post hoc analysis (from Latin post hoc, "after this") consists of statistical analyses that were specified after the data were seen.

PRRs: pattern recognition receptors

qHSCs: quiescent hepatic stellate cells

ROS: reactive oxygen species

SCD1: stearoyl-coenzyme A desaturase 1

SVR: sustained virologic response

THR-β: thyroid hormone receptor beta

TNF-α: tumour necrosis factor-alpha

Conflict Of Interest

All authors declare no conflicts of interest.

Authors Contribution

Authors have equally participated and shared every item of the work.

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