

Liver Fibrosis: A Clinical Update

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Abstract

Liver fibrosis is a disease that affects patients with hepatitis B virus or hepatitis C virus, harmful alcohol consumption levels, and nonalcoholic fatty liver disease. It is important to assess the cause, disease severity, and prognosis at the time of presentation to determine suitable treatment. The aim of this review article is to outline the recent advances in the diagnosis, management, and treatment of liver fibrosis. A PubMed review was performed encompassing the years 1982–2019 using the following search terms: ‘liver fibrosis’, ‘hepatitis C virus’, ‘hepatitis B virus’, ‘non-alcoholic fatty liver disease’, and ‘alcoholic liver disease’. Results showed that the cornerstone therapy for liver fibrosis is to remove the offending agent and treat the underlying disease. The gold standard method of diagnosis is liver biopsy; however, this procedure is invasive and thus multiple laboratory and radiologic tests are used to help determine the degree of fibrosis. There are few pharmacological agents known to treat fibrosis and they are disease specific. For example, the only proven therapy for fibrosis improvement in alcoholic liver disease is abstinence. The authors concluded that liver fibrosis carries a high morbidity and mortality risk with few therapeutic options depending on the cause and degree of fibrosis. Larger multicentre prospective studies are needed to examine effective agents to prevent, stop, or reduce fibrosis.

INTRODUCTION

Liver fibrosis is the common sequelae of chronic insult to the liver from any aetiology. The most common causes are alcohol-related, fatty liver disease, chronic hepatitis B or C viral infections, autoimmune hepatitis, and metabolic or genetic liver diseases. The disease spectrum of liver fibrosis ranges from non-cirrhotic (stages FO–F3) to cirrhotic (stage F4). Fibrosis is the replacement of tissue with a collagenous scar as a result of repetitive liver insults. Cirrhosis is the end stage

of liver fibrosis resulting in regenerative nodular hepatic echotexture surrounded by fibrotic bands and distortion of hepatic vasculature.^{1,2} Liver fibrosis is a major cause of morbidity and mortality.³ A survey by the Centers for Disease Control and Prevention in 2016 found that there were 4.9 million people living with liver disease.⁴ Chronic liver disease and cirrhosis is the sixth leading cause of all-cause mortality in people aged 25–64 years.⁵ Patients may be asymptomatic or present with a wide range of symptoms, including decompensation and liver failure. Liver biopsy is the gold standard for

diagnosis; however, many recent advances in biomarkers and imaging are being used as non-invasive methods of diagnosis.⁶ Rates of fibrosis differ depending on the type of insult, age, and sex.⁷ Liver fibrosis was previously thought to be a unidirectional process, but many clinical studies have shown that it is a dynamic process with potential for reversibility. The goal of current and future therapies for any chronic liver disease is to prevent, reduce, and reverse the progression of fibrosis to cirrhosis with its complications and the need for liver transplantation.^{8,9} This review will discuss the current and future advances in the diagnosis, management, and treatment of liver fibrosis.

CLINICAL PRESENTATION

Liver fibrosis often goes unrecognised unless the patient manifests symptoms from complications of cirrhosis. When a patient presents with liver disease, it is important to exclude or confirm cirrhosis, especially when the presentation is with incidental findings of elevated serum aminotransferases, unexplained thrombocytopenia, or abnormal liver imaging. Risk factors for developing liver fibrosis include metabolic syndrome, heavy alcohol consumption, exposure to hepatotoxic substances, and the use of hepatotoxic medications.¹⁰ Thus, a careful clinical history and index of suspicion is important to identify the disease early. Physical exam findings that assist with diagnosis include jaundice, spider angioma,¹¹ a nodular liver on palpation,¹⁰ splenomegaly, ascites,¹² caput medusae, palmar erythema, gynecomastia,¹³ asterix,² and Type 2 diabetes.¹⁴ However, many patients are without physical findings and advanced fibrosis is diagnosed by abnormalities on haematological, biochemical, endoscopic, or radiologic evaluation.^{2,15}

PATHOPHYSIOLOGY

Fibrosis is a wound-healing process that becomes dysregulated when repeated insults result in pathologic, chronic fibrinogenesis.¹⁶ The common aetiologic agents for chronic repetitive liver damage are harmful alcohol consumption, metabolic syndrome and diabetes, viral infections with hepatitis C virus (HCV) or hepatitis B virus (HBV), toxins and drugs, and autoimmune or

metabolic diseases.^{17,18} All liver cell lines undergo alterations in phenotype due to changes in the microenvironment in the space of Disse.¹⁹ The hepatic stellate cell (HSC) is the major driver of hepatic fibrosis followed by portal fibroblasts and bone-marrow derived fibrocytes. Extracellular signals from the innate and adaptive immune systems, such as Kupffer cells, macrophages, natural killer cells, T cells, and B cells, modulate HSC activation, also known as the initiation phase.^{18,20} In early liver injury, endothelial cells produce a variant of fibronectin that also stimulates HSC activation.¹⁹ Hepatocytes stimulate activation through lipid peroxidases leading to oxidative stress, and Kupffer cells stimulate matrix synthesis, cell proliferation, and the release of retinoids by stellate cells.¹⁹ HSC release chemokines and cytokines that recruit and activate inflammatory immune cells, contributing to the perpetuation phase of fibrogenesis. In this phase, the HSC proliferate and lead to contractility, fibrogenesis, chemotaxis, matrix degradation, retinoid loss, and cytokine release.^{18,19} Stellate cell mitogens, such as platelet derived growth factor, endothelin-1, thrombin, fibroblast growth factor, and insulin-like growth factor lead to proliferation. Endothelin-1, along with arginine vasopressin, adrenomedullin, and eicosanoids, activate HSC to increase portal pressures and resistance by constricting sinusoids and contracting the liver. Transforming growth factor B1 is the primary fibrinogenic factor and is upregulated by the transcription factors Sp1 and Zf9. Other factors involved in fibrinogenesis include TNF, lipid peroxides, and acetaldehyde.¹⁹ The extracellular matrix, which is made up of molecules such as collagens, glycoproteins, proteoglycans, and glycosaminoglycans, further promotes HSC activation. When the liver becomes fibrotic, the interstitial collagen increases 3–8-fold, a concept known as ‘capillarisation’ that causes destruction of hepatocyte microvilli and endothelial fenestrations.¹⁹ As a result, the transport of important solutes to hepatocytes is impaired, leading to hepatic dysfunction.²¹ Stellate cells are a known source of matrix metalloproteinase-2. Matrix metalloproteinases have been identified as responsive for extracellular matrix remodelling; however, their regulators have not been identified.¹⁹ HSC activation and proliferation can be inhibited and even reversed. Mechanisms of reversal involve apoptosis, immune elimination,

senescence, and reversion to an inactivated state.^{20,22} These pathways are promising targets for novel therapeutic agents.

DIAGNOSIS

Diagnosing and assessing the degree of liver fibrosis is important in predicting liver-related morbidity and mortality and the emergence of complications of portal hypertension.²³ Histologic scoring systems have been developed to grade (degree of inflammation that reflects ongoing liver disease injury) and stage (amount of current fibrosis) the extent of hepatic disease. The major determinants of inflammatory activity are lymphocytic piecemeal necrosis, lobular necroinflammation, and portal inflammation, which are graded 0–4 in most classification systems. The degree of fibrosis is based on the

expansion of fibrotic areas between portal tracts. Stages of fibrosis can range from 0–4 or 0–6 depending on which staging system is used. There are multiple validated scoring systems, including Scheuer/Batts–Ludwig/Tsui which grades on a scale of 0–4; METAVIR, on a scale of 0–4; and Ishak et al.,²⁴ on a scale of 0–6 (Table 1). There are invasive and non-invasive methods of staging for liver fibrosis (Table 2). Combination testing may be a more effective prognostic tool when compared to any individual non-invasive method. In one study, the aspartate aminotransferase (AST)-to-platelet ratio index (APRI), in combination with ultrasound, had a positive predictive value of 80%.^{27,28}

Liver Biopsy

Liver biopsy for diagnosis of cirrhosis is needed when the diagnosis is uncertain based on clinical or biochemical and radiological assessment.^{10,27}

Table 1: Fibroscan evidence-based cut-off references.

	*Bonder-Afdahl ²⁵	*Tapper-Castera-Afdahl ²⁶
HBV	F0-F1 ≤6.0	Significant fibrosis ≥9.0
	F2 >6.0	
	F3 ≥9.0	Cirrhosis ≥11.7
	F4 ≥12.0	
HCV (HCV and HIV)	F0-F1 ≤7.0 (≤7.0)	Significant fibrosis ≥7.3
	F2 >7.0 (≤10.0)	
	F3 ≥9.5 (≥11.0)	Cirrhosis ≥12.5
	F4 ≥12.0 (≥14.0)	
NAFLD/NASH	F0-F1 ≤7.0	Cirrhosis ≥10.3
	F2 ≥7.5	
	F3 ≤10.0	
	F4 ≥14.0	
Alcoholic liver disease	Abstinent	Cirrhosis ≥12.5
	Drinking	Cirrhosis ≥22.7
Cholestatic	F0-F1 ≤7.0	Cirrhosis ≥17.9
	F2 ≥7.5	
	F3 ≥10.0	
	F4 ≥17.0	

*Bonder–Afdahl and Tapper–Castera–Afdahl are names of studies validating different techniques for measuring degree of fibrosis when using Fibroscan.

HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic fatty steatohepatitis.

Table 2: Assessing the degree of liver fibrosis.

	Pros	Cons
Liver biopsy	Most accurate diagnosis.	Invasive; intra-observer variability.
Scoring Systems		
ARR, APRI, Fib-4, UIC	Uses standard laboratory tests.	Cannot discriminate the intermediate stages of fibrosis.
FibroTest	Uses software algorithm and adjusts for age and sex with applicability of 99%.	Does not detect significant fibrosis or cirrhosis; need to combine with other methods.
Hepascore	Computer-based score adjusted for sex and age.	Not useful in NAFLD or those co-infected with HIV.
Fibrospect-II	Computer generated.	Overestimates in African Americans and HCV.
Imaging		
Fibroscan	Accurate and reproducible.	Limited in obesity and acute inflammatory flares.
ARIF	Only requires standard equipment.	Operator dependent.
SWE	Higher accuracy than TE or ARIF.	Operator dependent.
MRE/MRI	More sensitive and specific than most other non-invasive tests, less operator dependent.	Time-consuming and costly.

APRI: aspartate aminotransferase-to-platelet ratio index; ARIF: acoustic radiation force impulse; ARR: alanine aminotransferase ratio; Fib-4: fibrosis-4; HCV: hepatitis C virus; MRE: magnetic resonance enterography; NAFLD: nonalcoholic fatty liver disease; SWE: shear wave elastography; TE: transient elastography; UIC: Universal Index for Cirrhosis.

In patients diagnosed with cirrhosis, the liver biopsy is sometimes performed for underlying aetiology of the disease, especially to rule out treatable diseases, such as autoimmune hepatitis. Biopsy can be obtained through a transthoracic, subcostal, or transvenous approach and can assist with diagnosis, prognosis, and management, particularly in those with atypical features or co-existing disorders.²³ In a recent prospective study of 176 patients, liver biopsy changed the diagnosis in 55 (31.2%) patients.²⁹ However, there are risks associated with liver biopsy. In a retrospective study by Chi et al.³⁰ there was a 6.00% rate of overall complications, most frequently pain followed by excessive bleeding with an overall risk of death of 0.03%. Absolute contraindications include an uncooperative patient, severe coagulopathy, infection of the hepatic bed, and extrahepatic biliary obstruction. Relative contraindications include ascites, morbid obesity, possible vascular lesion, amyloidosis, and hydatid disease.²⁹

Non-Invasive Measures of Fibrosis

Given the invasiveness and potential for complications with liver biopsy, non-invasive methods to assess the stage of hepatic fibrosis are increasingly being used in clinical practice. The most common modalities include elastography using ultrasound and magnetic resonance technology, as well as measurement of serum biomarkers. Transient elastography (TE), or Fibroscan (Table 1), is an accurate and reproducible method to detect liver fibrosis using ultrasound that can be performed in the outpatient setting. It is also a successful predictor of fibrosis complications such as portal hypertension and hepatocellular carcinoma (HCC).³¹ The transducer propagates vibrations of low amplitude (50 Hz) to the liver, and the velocity of this propagation is used to determine tissue stiffness. However, the accuracy of TE is limited in obese patients.³² The sensitivity and specificity for the diagnosis of significant fibrosis, advanced

fibrosis, and cirrhosis in chronic hepatitis B is 71.6% and 81.6%, 79% and 84.6%, and 80% and 86.6%, respectively, with an overall sensitivity and specificity of 83% and 89%^{33,34} (Table 1). TE in HCV has an area under the curve of receiver operating characteristic (AUROC) from 0.77–0.90, with a cut-off value of 6.20–8.70 kPa for assessment of significant fibrosis ($F \geq 2$); HBV, AUROC, 0.81–0.95; cut off value, 6.30–7.90 kPa; primary biliary cirrhosis (PBC), primary sclerosing cholangitis, and Wilson's disease, AUROC range is 0.81–0.95 for significant fibrosis.³⁵ TE has also been validated in nonalcoholic fatty liver disease (NAFLD)³⁶ and alcoholic liver disease (ALD).³⁷ However, TE overestimates the degree of fibrosis in the setting of inflammatory activity. Thus, if a patient is in an acute flare, it is recommended to wait until alanine aminotransferase (ALT) levels have stabilised.³⁵

Acoustic radiation force impulse (ARIF) of the liver is an additional ultrasonographic method to measure liver fibrosis, with a sensitivity and specificity of 84% and 92%, respectively, and only requires standard ultrasound equipment. However, it is operator dependent.^{34,38}

2D-shear wave elastography (SWE) is a real-time technique that produces a colour-coded image from radiation generated by an amplitude modulated beam of focussed ultrasound.³⁹ A recent meta-analysis proposed that SWE may be an equally helpful method for detecting liver fibrosis and may have higher accuracy than TE and ARIF at detecting fibrosis severity.³⁹ The pooled sensitivity and specificity for the varying stages of fibrosis are 85% and 81% for F2 or greater, 90% and 81% for F3 or greater, and 87% and 88% for F4 or greater.⁴⁰ However, this method is also operator dependent. As with ARIF, the operator has the potential to influence the findings based on where they place the region of interest, as opposed to TE where this variability in operator technique is not present.⁴¹

Magnetic resonance elastography is a contrast phase study that uses mechanical wave propagation to assess tissue stiffness and can also be used to assess portal hypertension and spleen stiffness simultaneously. The sensitivity in chronic hepatitis B in significant fibrosis, advance fibrosis, and cirrhosis were 92.8% and 93.7%, 89.6% and 93.2%, and 89.5% and 92%, respectively.³³ Overall sensitivity and specificity

is 100% and 96%, respectively.³⁴ Although more sensitive and specific than the other non-invasive tests with less operator-variability, this method is more time-consuming and costly than the other imaging modalities.⁴²

Serological Markers

These biomarkers for assessing fibrosis stage can be based on tests specifically used for this purpose or tests needed for standard of care.

Markers Based on Standard of Care

Laboratory Parameters

Markers based on standard of care include many scoring systems, such as aminotransferase-to-ALT ratio (ARR),⁴³ APRI,⁴⁴ and fibrosis-4 (FIB-4).⁴⁵ One of the most commonly used formulas, APRI, is calculated using the patient's AST level, corrected for the upper limit of normal, and platelet count. When combining serum ferritin (SF) with the AAR, APRI, FIB-4, and Fibro-Q, SF plus APRI was the most reliable to predict cirrhosis.⁴³ On the other hand, the Universal Index for Cirrhosis (UIC) had the highest AUROC when compared to Fibro-Q, FIB4, APRI, and ARR, and can be used in all types of fibrosis.⁴⁶ Fibro-mark was found to be a superior predictor of fibrosis over existing scores in those with chronic HCV.⁴⁷ The NAFLD fibrosis score uses routine demographic and laboratory variables, such as age, glucose level, BMI, platelet count, albumin, and AST/ALT to differentiate those with advanced fibrosis with an AUROC of 0.88 and 0.82.⁴⁸ In addition, the BARD score is able to determine advanced fibrosis at stages F3 and F4, with a negative predictive value of 97%.⁴⁹ While accurate in excluding or confirming significant fibrosis, these formulas often fail to discriminate the intermediate stages of fibrosis necessitating the use of other non-invasive methods.

Markers Requiring Special Tests Outside Standard of Care Laboratory Parameters

FibroTest is a clinically validated measure of fibrosis that analyses serum biomarkers ($\alpha 2$ -macroglobulin, apolipoprotein A1, haptoglobin, gamma-glutamyl-transpeptidase, and total bilirubin) and uses a software algorithm to determine an individual score while adjusting for age and sex at a mean applicability rate of 99.03%.⁵⁰ However, it is limited in detecting

MANAGEMENT (TABLE 3)

significant fibrosis and cirrhosis and thus it is recommended to combine with other methods of diagnosis to improve accuracy.⁵¹

Hepascore is another computed-based fibrosis score adjusted for sex and age that analyses serum levels of total bilirubin, gamma-glutamyl transferase, α 2-macroglobulin, and serum hyaluronic acid (HA). This test has been used as a primary screening method to determine the need for liver biopsy due to its ability to predict the level of fibrosis, particularly cirrhosis.⁵² Hepascore has shown better diagnostic predictability in HCV, HBV, and ALD than for NAFLD and those co-infected with HIV.⁵³

FIBROspect-II (FS-II) uses α -2 macroglobulin, HA, and tissue inhibitor metalloproteinase type 1 to estimate liver fibrosis.⁵⁴ However, FS-II may overestimate degree of fibrosis in African Americans with HCV.⁵⁵ In one study, HA was equally as effective at determining the stage of fibrosis in HCV as compared with the FS-II score and, thus, may be a more cost-effective alternative for screening.⁵⁶

Enhanced liver fibrosis score uses procollagen III amino terminal peptide, HA, and tissue inhibitor of metalloproteinase I and can allow for the avoidance of liver biopsy in approximately 60% of patients.⁵⁷

Table 3 summarises effective therapies for the reduction of liver fibrosis in patients with various diseases.

General Management

Preventive hepatology focusses on nutrition; promoting a healthy lifestyle, including exercise and abstinence from alcohol consumption; vaccinations; and screening for HCC. Malnutrition is a frequent complication in chronic liver disease and, along with obesity and sarcopenia, can lead to a worse prognosis.⁶⁹ Dietary interventions should be individualised and may focus on nutritional micronutrient replacement, adequate protein calorie intake of 1.2-1.5 g/kg daily, and low sodium consumption. Common micronutrient deficiencies include thiamine, B12, folic acid, retinol, vitamin K, vitamin D, zinc, selenium, and magnesium. Patients should consume 5-7 small meals per day to prevent consumption of too much protein in a single meal. Some may benefit from a late-night snack due to the evidence supporting improvement in sarcopenia and quality of life.⁷⁰ In patients that are overweight, weight loss has been proven to not only improve ALT/AST and insulin resistance but also quality of life in ALD and HCV liver disease patients.⁷¹

Table 3: Therapy proven to aid in fibrosis regression.

HBV	Tenofovir alafenamide, tenofovir disoproxil fumarate with adefovir dipivoxil ^{58,59}
	Entecavir ⁶⁰
	Lamivudine ⁶¹
HCV	Interferon-derived therapy ⁶²
	Direct-acting anti-virals ⁶³
NAFLD	Obeticholic acid ⁶⁴
	Selonsertib ⁶⁵
Alcoholic liver disease	Abstinence from alcohol ⁶⁶
Autoimmune hepatitis	Corticosteroids and azathioprine ⁶⁷
Primary biliary cirrhosis	Ursodiol ⁶⁸

HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: nonalcoholic fatty liver disease.

Recommended vaccinations, other than those recommended for the general population, include hepatitis A and B and pneumococcal vaccinations, regardless of age.⁷² Screening for oesophageal varices begins once the diagnosis of cirrhosis is made.⁷³ HCC screening is also typically performed once a patient has developed cirrhosis; however, there is increasing evidence to support the need for screening in those with earlier stages of fibrosis. In recent studies, the incidence of HCC in those without cirrhosis was found to be elevated in those with HBV, NAFLD, and metabolic syndrome.^{74,75} However, those with F3 fibrosis have much lower cost-effectiveness for screening, as well as a decreased risk for development of liver disease complications and better survival than patients with cirrhosis (F4 fibrosis).⁷⁶ Portal hypertension is a complication of advanced liver fibrosis that can result in variceal bleeding and ascites. Once a patient develops cirrhosis, a variceal screening oesophagogastroduodenoscopy should be performed and repeated after 1–3 years, depending on findings.⁷⁷

The most effective way to manage hepatic fibrosis is to eliminate the stimulus or harmful cause of hepatic damage, but this is not always feasible. No anti-fibrotic agents have been approved for human use that work effectively at eliminating or reducing fibrosis in the clinical setting. Due to the disease complexity, it is suspected that combination therapy may be needed to target two pathways to effectively treat fibrosis and cirrhosis.⁷⁸ The current mainstay of treatment for liver fibrosis is to treat the underlying disease.⁸

Hepatitis B Virus Infection

Long term suppression of chronic HBV can lead to regression of fibrosis and cirrhosis. Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir and, when compared to adefovir dipivoxil as single therapy for chronic HBV, demonstrated a significantly greater number of complete responders at 48 weeks, defined as HBV DNA <400 copies/mL and histological improvement (reduction of ≥ 2 points in Knodell necroinflammatory score).⁷⁹ In a study of patients randomised to TDF with adefovir dipivoxil, 87% had histological improvement and 51% had regression of fibrosis at Week 240 ($p < 0.0001$). In addition, of the 96 patients with cirrhosis, 74% no longer had cirrhosis and only 3 of 252

patients progressed to cirrhosis at 5 years ($p < 0.0001$).⁵⁸ Both nucleoside-naïve patients who were treated with entecavir⁶⁰ and patients treated with lamivudine therapy⁶¹ had significant histological improvement and regression of fibrosis or cirrhosis. Furthermore, anti-viral therapy significantly improves decompensated cirrhosis, as well as liver function and mortality rates.⁸⁰ Tenofovir alafenamide is a prodrug that was developed to allow more efficient delivery of the active metabolite than TDF and had greater reductions in FibroTest scores at 48 weeks (mean change 0.07 versus 0.04; $p = 0.007$).⁵⁹ It is important to continue HCC screening because HCC in serologically cured HBV can occur in those with pre-cirrhosis or cirrhosis.⁸¹ However, those with F3 fibrosis have much lower cost-effectiveness for screening as well as decreased risk for development of liver disease complications and better survival than patients with cirrhosis (F4 fibrosis).⁷⁶

Hepatitis C Virus Infection

Historically, HCV infection was treated with interferon and ribavirin. Interferon-derived therapy resulted in a 50% regression in cirrhosis in the 30% who achieved a sustained virologic response (SVR). However, in those with advanced cirrhosis, only 5% saw regression of their liver disease over a 10 year period.⁶² Lower baseline stage of fibrosis, sustained viral response, age <40 years, BMI <27, and viral load <3.5 million copies per mL were independently associated with regression of fibrosis after treatment.⁸²

The newer direct-acting antivirals (DAA) may eradicate HCV, but have not yet been proven to improve survival and complications.⁸³ In a prospective study of 70 patients, 48.6% had a >30% improvement in vibration-controlled TE.⁷⁴ In another prospective study of 304 patients, TE was used to assess the degree of fibrosis after DAA therapy and showed that 65.1% achieved at least a 20% reduction in liver stiffness.⁸⁴ Another study of 260 patients on DAA showed a significant fibrosis regression in 40% with baseline advanced fibrosis versus mild fibrosis (52.3 versus 22.5%; $p < 0.001$).⁸⁵ Larger prospective trials are needed to further confirm these results. Furthermore, it is difficult to determine their effect on regression of fibrosis and cirrhosis because liver biopsy is not commonly used. TE may overestimate the degree of regression of

disease and is thought to falsely show lower fibrosis staging due to decreased inflammation once the virus is cleared.^{63,86} Data matching TE and liver biopsy after SVR is lacking and it is unclear how long a patient will need monitoring after SVR. As with HBV clearance, those with HCV clearance will also need follow-up for HCC.⁸⁷ Some patients with HCV were even seen to have an unexpected high recurrence rate of HCC at 27-29% after treatment with ablation or radiation. This study suggests this population receiving DAA may need closer screening.⁸⁸ However, in the age of DAA, a reduction of 30-50% was seen in those with HCV requiring wait-listing and subsequently liver transplant, indicating a tremendous success with these medications. Furthermore, there are approximately 600 donor livers each year now being allocated to other forms of chronic liver disease.^{89,90}

Nonalcoholic Fatty Liver Disease

The only proven treatment for NAFLD is lifestyle modification, including control of the components of metabolic syndrome. Thus, therapy is directed at controlling risk factors such as insulin resistance, decreasing delivery of fatty acids to the liver, and the use of hepatoprotective medications.⁹¹ Weight loss improves histologic features of NAFLD, particularly nonalcoholic fatty steatohepatitis (NASH). The highest rate of their reduction is seen in those who lose >10% of bodyweight, with 90% resolution of NASH and 45% regression of fibrosis.⁹² In a recent study, a text messaging approach encouraging a healthy lifestyle improved weight loss and hepatic function tests in patients with NAFLD.^{92,93} In another study, some patients with only 3.0-4.9% weight loss achieved remission of NAFLD at 12 months.⁹⁴ Previously, NASH was thought to increase the risk of adverse outcomes, but, in a randomised retrospective study of 646 biopsy-proven patients with NAFLD, the stage of fibrosis rather than NASH was determined to predict adverse related events.⁹⁵ Furthermore, it is suggested that fibrosis stage should be part of predicting all-cause mortality secondary to cardiovascular disease and development of chronic kidney disease.^{96,97}

There is currently no U.S. Food and Drug Administration (FDA) approved medication for the treatment of NAFLD or NASH, but multiple trials are underway. A meta-analysis

of thiazolidinediones in the treatment of NASH showed significant histological improvement in ballooning degeneration, lobular inflammation, and steatosis, although this is at the expense of significant weight gain.⁹⁸ A Bayesian network meta-analysis found that thiazolidinediones, vitamin E, pentoxifylline, and obeticholic acid (OCA) improve ballooning degeneration, lobular inflammation, and steatosis, while only pentoxifylline and OCA improve fibrosis.⁶⁴ A Phase III, randomised, double-blind, placebo-controlled trial (REGENERATE)⁹⁹ is being conducted to assess the benefits of OCA in patients with NASH and advanced fibrosis. In the Phase IIb FLINT trial,¹⁰⁰ OCA demonstrated superiority over placebo based on an intention-to-treat ($p=0.0002$) in addition to improving liver fibrosis ($p=0.004$) in NASH and was well tolerated.⁶⁵ AURORA is a Phase III, randomised, double-blind, placebo-controlled study on cenicriviroc for the treatment of liver fibrosis for those with NASH.¹⁰¹ RESOLVE-IT is a Phase III multicentre study looking at the effects of elafibranor in patients with NASH and fibrosis.¹⁰² Selonsertib was studied in a Phase II trial¹⁰³ with NASH patients and was determined to be superior to placebo in improvement of one stage of fibrosis or greater, and improved fibrosis without worsening NASH.⁶⁵ STELLAR 3¹⁰⁴ and STELLAR 4¹⁰⁵ are Phase III studies examining selonsertib in those with NASH F3 and compensated F4 fibrosis, respectively. ATLAS¹⁰⁶ is a Phase II study examining selonsertib, firsocostat, and cilofexor, both individually and in combinations, in patients with bridging fibrosis or NASH; the results of this study have thus far been promising, with minimal side effects and a reduction of 30% measured hepatic fat based upon MRI.

Alcoholic Liver Disease

The mainstay of treatment for ALD is a reduction in alcohol use.⁶⁶ Abstinence can lead to total resolution of hepatic steatosis with the most benefits seen in patients with jaundice or ascites. Abstainers' probability of survival was found to be 87% compared to 55% in persistent drinkers.¹⁰⁷ A recent study suggested in those with NAFLD, even moderate alcohol consumption (10.0-29.9 g per day for men and 10.0-19.9 g per day for women) can result in worsening fibrosis.¹⁰⁸ Corticosteroids have been studied in both ALD

and alcoholic hepatitis (AH), although results are variable. Prednisolone studied in the STOPAH trial did not show a mortality benefit at 90 days or at 1 year in patients with severe AH.¹⁰⁹ However, the American Association for the Study of Liver Diseases (AASLD) and the American College of Gastroenterology (ACG) recommend a trial of steroids in patients with severe AH because of the trend for 28-day mortality benefit among STOPAH participants in the prednisolone therapy arm.^{66,110} Oxidative stress is an important component in the pathology of ALD; however, antioxidants like s-adenosyl-L-methionine, vitamin E, and silymarin have failed to show efficacy in the treatment of ALD.¹¹¹

A Phase II study of livercellgram,¹¹² a stem cell therapy, is being conducted in patients with ALD. Many ongoing clinical trials for ALD are focussed on targeting the gut–liver axis (probiotics, antibiotics, zinc), inflammation and oxidative stress (anakinra, extracorporeal cellular therapy, ASK-1 inhibitor selonsertib, and metadoxine), and regenerative agents (G-CSF and IL-22).^{110,113–120} There is a growing interest in investigating the use of probiotics in ALD due to its close association with gut microbial alterations; however, the precise mechanism needs further investigation.¹²¹ A current Phase II trial¹²² is investigating rifaximin in ALD. The remainder of clinical trials focus on AH. Selonsertib (ASK-1 inhibitor) has completed a Phase II trial¹²³ with prednisolone versus selonsertib alone in those with AH and data is currently pending. Metadoxine showed improvement in 3 and 6-month mortality in those with severe AH, aided with alcohol abstinence.¹²⁴ A Phase IV trial¹²⁵ is underway investigating the efficacy of G-CSF in patients with severe AH. IL-22 is overexpressed in liver regeneration and repair, and a current Phase II trial¹²⁶ is underway evaluating the use of IL-22 in AH.

Autoimmune Hepatitis

Corticosteroids and anti-inflammatory agents are the mainstay of treatment for autoimmune hepatitis. In those with mild disease, a low dose of prednisone may be used, such as 30 mg daily. In those with more severe hepatitis, the recommendation is to begin with a higher dose of 60 mg prednisone daily. If patients are at increased risk of side effects (brittle diabetes, post-menopausal women, hypertension, emotional lability, obesity, or osteoporosis), a

low dose of prednisone (30 mg daily) combined with azathioprine (50 mg daily) is used for initial treatment. If a patient has significant cytopenia, is pregnant, or has a malignancy, azathioprine should be avoided. Corticosteroids have been shown to improve or stabilise fibrosis in about two-thirds of patients.⁶⁷ If continued on steroids, patients should be monitored closely with annual bone densitometry and should also receive hepatitis A and B virus vaccinations, regardless of age.¹²⁷

Primary Biliary Cirrhosis

Although PBC is thought to be a form of autoimmune disease, immunosuppressive therapy has not proven beneficial in this population. Ursodeoxycholic acid (UDCA) is the mainstay of treatment and has been shown to delay the time of the liver transplant and death in patients with PBC.¹²⁸ Although UDCA effectively decreases AST and ALT, it did not appear to improve existing cholestasis or fibrosis compared to placebo in one study.¹²⁹ However, in another study, UDCA was found to significantly delay the progression of fibrosis in PBC with 76% on UDCA remaining in early stage disease versus 29% in the placebo group.⁶⁸ Furthermore, the decreased need for ALT among all aetiologies for PBC treated with UDCA support its use.¹³⁰

OCA showed benefits as monotherapy or in conjunction with UDCA over placebo in patients with PBC in single centre studies.¹³¹ COBALT, a Phase IV, double-blinded, randomised, placebo-controlled multicentre trial study is being conducted to further assess OCA in PBC.¹³² As HSC are the main drivers of liver fibrosis, they remain an important potential target for therapy. Although many drugs used in mouse models show improvement in liver fibrosis, medications targeting HSC have yet to be approved for the treatment of liver fibrosis.¹³³

SUMMARY

Common causes of hepatic fibrosis are chronic viral infection with HBV or HCV, harmful alcohol consumption, and NAFLD. With accelerating obesity rates worldwide and effective cure of HCV with DAA, alcohol and NAFLD are emerging as the leading causes of hepatic fibrosis and cirrhosis, with its related complications. Apart from treatment of the underlying aetiology and

risk factors, several new therapeutic approaches are being studied with potential to prevent, stop, or reverse the progression of liver fibrosis. The field is advancing rapidly, especially in NAFLD,

as many studies have consistently shown that fibrosis stage, and not fatty liver or inflammation severity, determines the long-term outcomes including hepatic and extra-hepatic outcomes.

References

- Friedman SL. Liver fibrosis -- From bench to bedside. *J Hepatol*. 2003;38(Suppl 1):S38-53.
- Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet*. 2008;371(9615):838-51.
- Hernandez-Gea V, Friedman SL. Pathogenesis of liver fibrosis. *Annu Rev Pathol*. 2011;6:425-56.
- Centers for Disease Control and Prevention. Summary Health Statistics Tables for U.S. Adults: National Health Interview Survey, 2017, Table A-4b, A-4c. Available at: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2017_SHS_Table_A-4.pdf. Last accessed: 1 May 2019.
- Centers for Disease Control and Prevention. Deaths: Final data for 2016, tables 6, 7. Available at: <https://www.cdc.gov/nchs/fastats/liver-disease.htm>. Last accessed: 1 May 2019.
- Patel K et al. Diagnosis of liver fibrosis: Present and future. *Semin Liver Dis*. 2015;35(2):166-83.
- Poynard T et al. A comparison of fibrosis progression in chronic liver diseases. *J Hepatol*. 2003;38(3):257-65.
- Bonis PA et al. Is liver fibrosis reversible? *N Engl J Med*. 2001;344(6):452-4.
- Cholankeril G, Ahmed A. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol*. 2018;16(8):1356-8.
- Wiegand J, Berg T. The etiology, diagnosis and prevention of liver cirrhosis: Part 1 of a series on liver cirrhosis. *Dtsch Arztebl Int*. 2013;110(6):85-91.
- Pirovino M et al. Cutaneous spider nevi in liver cirrhosis: Capillary microscopical and hormonal investigations. *Klin Wochenschr*. 1988;66(7):298-302.
- Cattau EL et al. The accuracy of the physical examination in the diagnosis of suspected ascites. *JAMA*. 1982;247(8):1164-6.
- Van Thiel DH et al. Liver disease and the hypothalamic pituitary gonadal axis. *Semin Liver Dis*. 1985;5(1):35-45.
- Williamson RM et al. Prevalence of and risk factors for hepatic steatosis and nonalcoholic fatty liver disease in people with type 2 diabetes: The Edinburgh type 2 diabetes study. *Diabetes Care*. 2011;34(5):1139-44.
- Peck-Radosavljevic M et al. Thrombopoietin induces rapid resolution of thrombocytopenia after orthotopic liver transplantation through increased platelet production. *Blood*. 2000;95(3):795-801.
- Schuppan D et al. Matrix as a modulator of hepatic fibrogenesis. *Semin Liver Dis*. 2001;21(3):351-72.
- Pinzani M. Pathophysiology of liver fibrosis. *Dig Dis*. 2015;33(4):492-7.
- Gandhi CR. Hepatic stellate cell activation and pro-fibrogenic signals. *J Hepatol*. 2017;67(5):1104-5.
- Li D, Friedman SL. Liver fibrogenesis and the role of hepatic stellate cells: New insights and prospects for therapy. *J Gastroenterol Hepatol*. 1999;14(7):618-33.
- Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol*. 2017;14(7):397-411.
- McGuire RF et al. Role of extracellular matrix in regulating fenestrations of sinusoidal endothelial cells isolated from normal rat liver. *Hepatology*. 1992;15(6):989-97.
- Huang Y et al. Modulation of hepatic stellate cells and reversibility of hepatic fibrosis. *Exp Cell Res*. 2017;352(2):420-6.
- Rockey DC et al.; American Association for the Study of Liver Diseases. Liver biopsy. *Hepatology*. 2009;49(3):1017-44.
- Garcia-Tsao G et al. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. *Hepatology*. 2010;51(4):1445-9.
- Bonder A, Afdhal N. Utilization of FibroScan in clinical practice. *Gurr Gastroenterol Rep*. 2014;16(2):372.
- Tapper EB et al. FibroScan (vibration-controlled transient elastography): Where does it stand in the United States practice. *Clin Gastroenterol Hepatol*. 2015;13(1):27-36.
- Lucero C, Brown RS. Noninvasive measures of liver fibrosis and severity of liver disease. *Gastroenterol Hepatol (N Y)*. 2016;12(1):33-40.
- Martin J et al. Accuracy of ultrasound and noninvasive markers of fibrosis to identify patients with cirrhosis. *Dig Dis Sci*. 2015;60(6):1841-7.
- Amarapurkar D, Amarapurkar A. Indications of liver biopsy in the era of noninvasive assessment of liver fibrosis. *J Clin Exp Hepatol*. 2015;5(4):314-9.
- Chi H et al. Multiple biopsy passes and the risk of complications of percutaneous liver biopsy. *Eur J Gastroenterol Hepatol*. 2017;29(1):36-41.
- Mikolasevic I et al. Transient elastography (FibroScan[®]) with controlled attenuation parameter in the assessment of liver steatosis and fibrosis in patients with nonalcoholic fatty liver disease - Where do we stand? *World J Gastroenterol*. 2016;22(32):7236-51.
- Wong GL. Update of liver fibrosis and steatosis with transient elastography (Fibroscan). *Gastroenterol Rep (Oxf)*. 2013;1(1):19-26.
- Xiao H et al. Comparison of diagnostic accuracy of magnetic resonance elastography and Fibroscan for detecting liver fibrosis in chronic hepatitis B patients: A systematic review and meta-analysis. *PLoS One*. 2017;12(11):e0186660.
- Sharma S et al. Non-invasive diagnosis of advanced fibrosis and cirrhosis. *World J Gastroenterol*. 2014;20(45):16820-30.
- Jung KS, Kim SU. Clinical applications of transient elastography. *Clin Mol Hepatol*. 2012;18(2):163-73.
- Hashemi SA et al. Assessment of transient elastography (FibroScan) for diagnosis of fibrosis in non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Caspian J Intern Med*. 2016;7(4):242-52.
- Nahon P et al. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. *J Hepatol*. 2008;49(6):1062-8.
- Takahashi H et al. Evaluation of acoustic radiation force impulse elastography for fibrosis staging of chronic liver disease: A pilot study.

- Liver Int. 2010;30(4):538-45.
39. Jiang T et al. Diagnostic accuracy of 2D-Shear wave elastography for liver fibrosis severity: A meta-analysis. *PLoS One*. 2016;11(6):e0157219.
 40. Li C et al. Diagnostic accuracy of real-time shear wave elastography for staging of liver fibrosis: A meta-analysis. *Med Sci Monit*. 2016;22:1349-59.
 41. Piscaglia F et al. Ultrasound shear wave elastography for liver disease. A critical appraisal of the many actors on the stage. *Ultraschall Med*. 2016;37(1):1-5.
 42. Wagner M et al. Magnetic resonance elastography of the liver: Qualitative and quantitative comparison of gradient echo and spin echo echoplanar imaging sequences. *Invest Radiol*. 2016;51(9):575-81.
 43. Afify SM et al. Five fibrosis biomarkers together with serum ferritin level to diagnose liver fibrosis and cirrhosis. *Clin Lab*. 2018;64(10):1685-93.
 44. Wai CT et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38(2):518-26.
 45. Teshale E et al. APRI and FIB-4 are good predictors of the stage of liver fibrosis in chronic hepatitis B: The chronic hepatitis cohort study (CHeCS). *J Viral Hepat*. 2014;21(12):917-20.
 46. Ahmed Z et al. Universal index for cirrhosis (UIC index): The development and validation of a novel index to predict advanced liver disease. *Hepat Med*. 2018;10:133-8.
 47. Attallah AM et al. Fibro-Mark: A panel of laboratory parameters for predicting significant fibrosis in chronic hepatitis C patients. *Br J Biomed Sci*. 2018;75(1):19-23.
 48. Angulo P et al. The NAFLD fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology*. 2007;45(4):846-54.
 49. Raszeja-Wyszomirska J et al. Validation of the BARD scoring system in Polish patients with nonalcoholic fatty liver disease (NAFLD). *BMC Gastroenterol*. 2010;10:67.
 50. Poynard T et al. Applicability and precautions of use of liver injury biomarker FibroTest. A reappraisal at 7 years of age. *BMC Gastroenterol*. 2011;11:39.
 51. Salkic NN et al. FibroTest/fibrosure for significant liver fibrosis and cirrhosis in chronic hepatitis B: A meta-analysis. *Am J Gastroenterol*. 2014;109(6):796-809.
 52. Kalantari H et al. Validation of hepascor as a predictor of liver fibrosis in patients with chronic hepatitis C infection. *Hepat Res Treat*. 2011;2011:972759.
 53. Huang Y et al. The ability of Hepascore to predict liver fibrosis in chronic liver disease: A meta-analysis. *Liver Int*. 2017;37(1):121-31.
 54. Zaman A et al. Assessment of FIBROSpect II to detect hepatic fibrosis in chronic hepatitis C patients. *Am J Med*. 2007;120(3):280.e9-14.
 55. Tama M et al. Overestimate of fibrosis by FIBROSpect® II in African Americans complicates the management of their chronic hepatitis C. *J Clin Transl Hepatol*. 2016;4(1):12-9.
 56. Mehta P et al. Diagnostic accuracy of serum hyaluronic acid, FIBROSpect II, and YKL-40 for discriminating fibrosis stages in chronic hepatitis C. *Am J Gastroenterol*. 2008;103(4):928-36.
 57. Wong GL et al. Non-invasive algorithm of enhanced liver fibrosis and liver stiffness measurement with transient elastography for advanced liver fibrosis in chronic hepatitis B. *Aliment Pharmacol Ther*. 2014;39(2):197-208.
 58. Marcellin P et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: A 5-year open-label follow-up study. *Lancet*. 2013;381(9865):468-75.
 59. Byrne R et al. Tenofovir alafenamide in the treatment of chronic hepatitis B virus infection: Rationale and clinical trial evidence. *Therap Adv Gastroenterol*. 2018;11:1756284818786108.
 60. Schiff ER et al. Long-term treatment with entecavir induces reversal of advanced fibrosis or cirrhosis in patients with chronic hepatitis B. *Clin Gastroenterol Hepatol*. 2011;9(3):274-6.
 61. Dienstag JL et al. Histological outcome during long-term lamivudine therapy. *Gastroenterology*. 2003;124(1):105-17.
 62. Grgurevic I et al. Hepatitis C is now curable, but what happens with cirrhosis and portal hypertension afterwards? *Clin Exp Hepatol*. 2017;3(4):181-6.
 63. Chan J et al. Direct-acting antiviral therapy for chronic HCV infection results in liver stiffness regression over 12 months post-treatment. *Dig Dis Sci*. 2018;63(2):486-92.
 64. Singh S et al. Comparative effectiveness of pharmacological interventions for nonalcoholic steatohepatitis: A systematic review and network meta-analysis. *Hepatology*. 2015;62(5):1417-32.
 65. Connolly JJ et al. Future pharmacotherapy for non-alcoholic steatohepatitis (NASH): Review of Phase 2 and 3 trials. *J Clin Transl Hepatol*. 2018;6(3):264-75.
 66. Singal AK et al. ACG clinical guideline: Alcoholic liver disease. *Am J Gastroenterol*. 2018;113(2):175-94.
 67. Borssén Å et al. Histological improvement of liver fibrosis in well-treated patients with autoimmune hepatitis: A cohort study. *Medicine (Baltimore)*. 2017;96(34):e7708.
 68. Corpechot C et al. The effect of ursodeoxycholic acid therapy on liver fibrosis progression in primary biliary cirrhosis. *Hepatology*. 2000;32(6):1196-9.
 69. EAftSolLEa, Liver EAftSot. EASL clinical practice guidelines on nutrition in chronic liver disease. *J Hepatol*. 2019;70(1):172-93.
 70. Silva M et al. Nutrition in chronic liver disease. *GE Port J Gastroenterol*. 2015;22(6):268-76.
 71. Hickman IJ et al. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. *Gut*. 2004;53(3):413-9.
 72. Alter MJ. Vaccinating patients with chronic liver disease. *Gastroenterol Hepatol (N Y)*. 2012;8(2):120-2.
 73. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: Variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. *Dig Dis*. 2016;34(4):382-6.
 74. Mittal S et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2016;14(1):124-31.e1.
 75. Chayanupatkul M et al. Hepatocellular carcinoma in the absence of cirrhosis in patients with chronic hepatitis B virus infection. *J Hepatol*. 2017;66(2):355-62.
 76. Axley P et al. Patients with stage 3 compared to stage 4 liver fibrosis have lower frequency of and longer time to liver disease complications. *PLoS One*. 2018;13(5):e0197117.
 77. Sauerbruch T et al. Managing portal hypertension in patients with liver cirrhosis. *F1000Res*. 2018;7.
 78. Trautwein C et al. Hepatic fibrosis: Concept to treatment. *J Hepatol*. 2015;62(1 Suppl):S15-24.
 79. Perry CM, Simpson D. Tenofovir disoproxil fumarate: In chronic hepatitis B. *Drugs*. 2009;69(16):2245-56.
 80. Jang JW et al. Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis. *Hepatology*. 2015;61(6):1809-20.

81. Tsuboi Y et al. Common clinicopathological features of the patients with chronic hepatitis B virus infection who developed hepatocellular carcinoma after seroconversion to anti-HBs--A consideration of the pathogenesis of HBV-induced hepatocellular carcinoma and a strategy to inhibit it. *Hepatogastroenterology*. 2006;53(67):110-4.
82. Poynard T et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology*. 2002;122(5):1303-13.
83. Jakobsen JC et al. Direct-acting antivirals for chronic hepatitis C. *Cochrane Database Syst Rev*. 2017;9:CD012143.
84. Dolmazashvili E et al. Regression of liver fibrosis over a 24-week period after completing direct-acting antiviral therapy in patients with chronic hepatitis C receiving care within the national hepatitis C elimination program in Georgia: Results of hepatology clinic HEPA experience. *Eur J Gastroenterol Hepatol*. 2017;29(11):1223-30.
85. Lledó GM et al. Regression of liver fibrosis after curing chronic hepatitis C with oral antivirals in patients with and without HIV coinfection. *AIDS*. 2018;32(16):2347-52.
86. D'Ambrosio R et al. The diagnostic accuracy of Fibroscan for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. *J Hepatol*. 2013;59(2):251-6.
87. Axley P et al. Hepatitis C virus and hepatocellular carcinoma: A narrative review. *J Clin Transl Hepatol*. 2018;6(1):79-84.
88. Ravi S et al. Unusually high rates of hepatocellular carcinoma after treatment with direct-acting antiviral therapy for hepatitis C related cirrhosis. *Gastroenterology*. 2017;152(4):911-2.
89. Flemming JA et al. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. *Hepatology*. 2017;65(3):804-12.
90. Belli LS et al.; The European Liver and Intestine Transplant Association (ELITA). Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. *J Hepatol*. 2018;69(4):810-7.
91. Sanyal AJ; Association AG. AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology*. 2002;123(5):1705-25.
92. Vilar-Gomez E et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015;149(2):367-78.
93. Axley P et al. Text messaging approach improves weight loss in patients with nonalcoholic fatty liver disease: A randomized study. *Liver Int*. 2018;38(5):924-31.
94. Wong VW et al. Community-based lifestyle modification programme for non-alcoholic fatty liver disease: A randomized controlled trial. *J Hepatol*. 2013;59(3):536-42.
95. Hagström H et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. *J Hepatol*. 2017;67(6):1265-73.
96. Dulai PS et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology (Baltimore, Md)*. 2017;65(5):1557-65.
97. Mutsaers HA et al. Chronic kidney disease and fibrosis: The role of uremic retention solutes. *Front Med (Lausanne)*. 2015;2:60.
98. Boettcher E et al. Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2012;35(1):66-75.
99. Intercept Pharmaceuticals. Randomized global Phase 3 study to evaluate the impact on NASH with fibrosis of obeticholic acid treatment (REGENERATE). NCT02548351. <https://clinicaltrials.gov/ct2/show/NCT02548351>.
100. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The farnesoid X receptor (FXR) ligand obeticholic acid in NASH treatment Trial (FLINT) (FLINT). NCT01265498. <https://clinicaltrials.gov/ct2/show/NCT01265498>.
101. Tobira Therapeutics Inc. AURORA: Phase 3 study for the efficacy and safety of CVC for the treatment of liver fibrosis in adults with NASJ. NCT03028740. <https://clinicaltrials.gov/ct2/show/NCT03028740>.
102. Genfit. Phase 3 study to evaluate the efficacy and safety of elafibranor versus placebo in patients with nonalcoholic steatohepatitis (NASH) (RESOLVE-IT). NCT02704403. <https://clinicaltrials.gov/ct2/show/NCT02704403>.
103. Gilead Sciences. Safety, tolerability, and efficacy of GS-4997 alone or in combination with simtuzumab (SIM) in adults with nonalcoholic steatohepatitis (NASH) and fibrosis stages F2-F3. NCT02466516. <https://clinicaltrials.gov/ct2/show/NCT02466516>.
104. Gilead Sciences. Safety and efficacy of selonsertib in adults with nonalcoholic steatohepatitis (NASH) and bridging (F3) fibrosis (STELLAR3). NCT03053050. <https://clinicaltrials.gov/ct2/show/NCT03053050>.
105. Gilead Sciences. Safety and efficacy of selonsertib in adults with compensated cirrhosis due to nonalcoholic steatohepatitis (NASH) (STELLAR 4). NCT03053063. <https://clinicaltrials.gov/ct2/show/NCT03053063>.
106. Gilead Sciences. Safety and efficacy of selonsertib, firsocostat, cilofexor, and combinations in participants with bridging fibrosis or compensated cirrhosis due to nonalcoholic steatohepatitis (NASH) (ATLAS). NCT03449446. <https://clinicaltrials.gov/ct2/show/NCT03449446>.
107. Bergheim I et al. Treatment of alcoholic liver disease. *Dig Dis*. 2005;23(3-4):275-84.
108. Chang Y et al. Nonheavy drinking and worsening of noninvasive fibrosis markers in nonalcoholic fatty liver disease: A cohort study. *Hepatology*. 2019;69(1):64-75.
109. Thursz MR et al. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med*. 2015;373(3):282-3.
110. O'Shea RS et al.; Practice Guideline Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Alcoholic liver disease. *Hepatology*. 2010;51(1):307-28.
111. Singal AK et al. Antioxidants as therapeutic agents for liver disease. *Liver Int*. 2011;31(10):1432-48.
112. Pharmicell Co., Ltd. Long-term follow-up study of Livercellgram in alcoholic LC patients who completed Livercellgram Phase 2 study. NCT02806011. <https://clinicaltrials.gov/ct2/show/NCT02806011>.
113. Peeraphatdit TB et al. Exploring new treatment paradigms for alcoholic hepatitis by extrapolating from NASH and cholestasis. *J Hepatol*. 2018;69(2):275-7.
114. Kang YJ, Zhou Z. Zinc prevention and treatment of alcoholic liver disease. *Mol Aspects Med*. 2005;26(4-5):391-404.
115. Shah VH. Managing alcoholic liver disease. *Clin Mol Hepatol*. 2015;21(3):212-9.
116. Thompson J et al. Extracorporeal cellular therapy (ELAD) in severe alcoholic hepatitis: A multinational, prospective, controlled, randomized trial. *Liver Transpl*. 2018;24(3):380-93.
117. Loomba R et al. The ASK1 inhibitor selonsertib in patients with nonalcoholic steatohepatitis: A randomized, phase 2 trial. *Hepatology*. 2017. [Epub ahead of print].
118. Caballería J et al. Metadoxine accelerates fatty liver recovery in alcoholic patients: Results of a randomized double-blind, placebo-control trial. Spanish Group for the Study of Alcoholic Fatty Liver. *J*

- Hepatol. 1998;28(1):54-60.
119. Singh V et al. Granulocyte colony-stimulating factor in severe alcoholic hepatitis: A randomized pilot study. *Am J Gastroenterol.* 2014;109(9):1417-23.
 120. Gao B, Shah VH. Combination therapy: New hope for alcoholic hepatitis? *Clin Res Hepatol Gastroenterol.* 2015;39 Suppl 1:S7-S11.
 121. Li F et al. Probiotics and alcoholic liver disease: Treatment and potential mechanisms. *Gastroenterol Res Pract.* 2016;2016:5491465.
 122. Hospital Universitari Vall d'Hebron Research Institute. Effects of rifaximin in patients with acute alcoholic hepatitis (RIFA-AAH). NCT02116556. <https://clinicaltrials.gov/ct2/show/NCT02116556>.
 123. Gilead Sciences. Selonsertib in combination with prednisolone versus prednisolone alone in participants with severe alcoholic hepatitis (AH). NCT02854631. <https://clinicaltrials.gov/ct2/show/NCT02854631>.
 124. Higuera-de la Tijera F et al. Metadoxine improves the three- and six-month survival rates in patients with severe alcoholic hepatitis. *World J Gastroenterol.* 2015;21(16):4975-85.
 125. Postgraduate Institute of Medical Education and Research. GCSF in alcoholic hepatitis. NCT03703674. <https://clinicaltrials.gov/ct2/show/NCT03703674>.
 126. Mayo Clinic. Use of F-652 in patients with alcoholic hepatitis (TREAT 008). NCT02655510. <https://clinicaltrials.gov/ct2/show/NCT02655510>.
 127. Manns MP et al. Diagnosis and management of autoimmune hepatitis. *Hepatology.* 2010;51(6):2193-213.
 128. Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. *Hepatology.* 2000;31(4):1005-13.
 129. Bellentani S et al. Ursodiol in the long-term treatment of chronic hepatitis: A double-blind multicenter clinical trial. *J Hepatol.* 1993;19(3):459-64.
 130. Lee J et al. Transplantation trends in primary biliary cirrhosis. *Clin Gastroenterol Hepatol.* 2007;5(11):1313-5.
 131. Nevens F et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med.* 2016;375(7):631-43.
 132. Intercept Pharmaceuticals. Phase 4 study of obeticholic acid evaluating clinical outcomes in patients with primary biliary cholangitis (COBALT). NCT02308111. <https://clinicaltrials.gov/ct2/show/NCT02308111>.
 133. Schon HT et al. Pharmacological intervention in hepatic stellate cell activation and hepatic fibrosis. *Front Pharmacol.* 2016;7:33.