Liver cirrhosis

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Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease. Recent advances in the understanding of the natural history and pathophysiology of cirrhosis, and in treatment of its complications, have resulted in improved management, quality of life, and life expectancy of patients. Liver transplantation remains the only curative option for a selected group of patients, but pharmacological treatments that can halt progression to decompensated cirrhosis or even reverse cirrhosis are currently being developed. This Seminar focuses on the diagnosis, complications, and management of cirrhosis, and new clinical and scientific developments.

Introduction

Fibrosis describes encapsulation or replacement of injured tissue by a collagenous scar. Liver fibrosis results from the perpetuation of the normal wound-healing response, resulting in an abnormal continuation of fibrogenesis (connective tissue production and deposition). Fibrosis progresses at variable rates depending on the cause of liver disease, environmental factors, and host factors.[1–3] Cirrhosis is an advanced stage of liver fibrosis that is accompanied by distortion of the hepatic vasculature. The resultant vascular distortion leads to shunting of the portal and arterial blood supply directly into the hepatic outflow (central veins), compromising exchange between hepatic sinusoids and the adjacent liver parenchyma—ie, hepatocytes. The hepatic sinusoids are lined by fenestrated endothelia that rest on a sheet of permeable connective tissue in the space of Disse, which also contains hepatic stellate cells and some mononuclear cells. The other side of the space of Disse is lined by hepatocytes that execute most of the known liver functions. In cirrhosis, the space of Disse is filled with scar tissue and endothelial fenestrations are lost, a process known as sinusoidal capillarisation.[4] Histologically, cirrhosis is characterised by vascularised fibrotic septa that link portal tracts with each other and with central veins, resulting in hepatocyte islands surrounded by fibrotic septa and that are devoid of a central vein (figure 1). The major clinical consequences of cirrhosis are impaired hepatocyte (liver) function, an increased intrahepatic resistance (portal hypertension), and the development of hepatocellular carcinoma. The general circulatory abnormalities in cirrhosis (splanchnic vasodilation, vasoconstriction and hypoperfusion of kidneys, water and salt retention, increased cardiac output) are intimately linked to the hepatic vascular alterations and resulting portal hypertension. Cirrhosis and its associated vascular distortion are traditionally regarded as irreversible but recent data suggest that cirrhosis regression or even reversal is possible.[5,6]

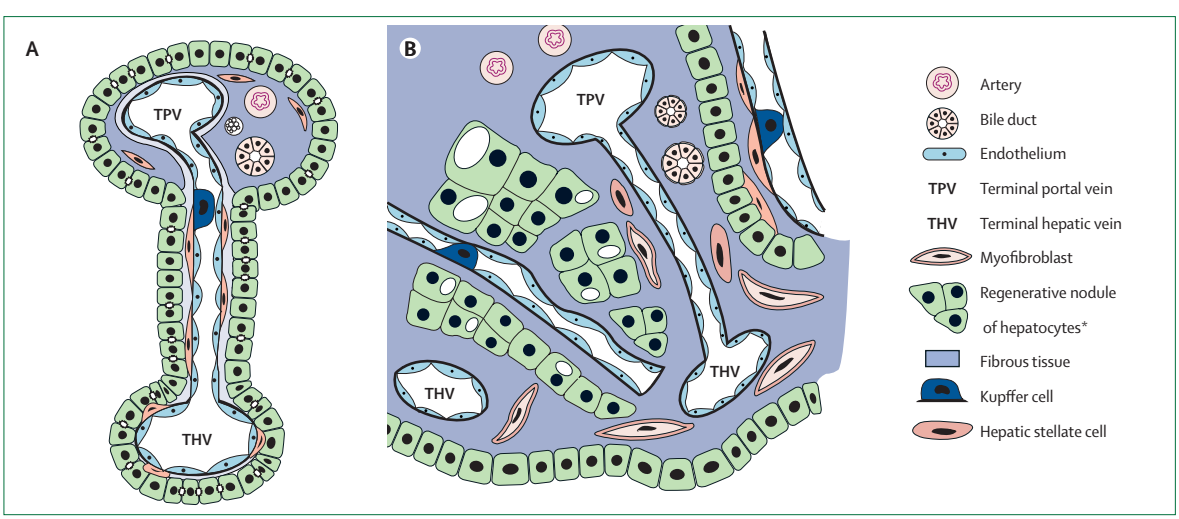

Figure 1: **Vascular and architectural alterations in cirrhosis**
Mesenteric blood flows via the portal vein and hepatic artery that extend branches into terminal portal tracts. (A) Healthy liver: terminal portal tract blood runs through hepatic sinusoids where fenestrated sinusoidal endothelia that rest on loose connective tissue (space of Disse) allow for extensive metabolic exchange with the lobular hepatocytes; sinusoidal blood is collected by terminal hepatic venules that disembogue into one of the three hepatic veins and finally the caval vein. (B) Cirrhotic liver: activated myofibroblasts that derive from perisinusoidal hepatic stellate cells and portal or central-vein fibroblasts proliferate and produce excess extracellular matrix (ECM). This event leads to fibrous portal-tract expansion, central-vein fibrosis and capillarisation of the sinusoids, characterised by loss of endothelial fenestrations, congestion of the space of Disse with ECM, and separation or encasement of perisinusoidal hepatocyte islands from sinusoidal blood flow by collagenous septa. Blood is directly shunted from terminal portal veins and arteries to central veins, with consequent (intrahepatic) portal hypertension and compromised liver synthetic function.

Epidemiology

The exact prevalence of cirrhosis worldwide is unknown. It was estimated at 0·15% or 400 000 in the USA,[7] which accounted for more than 25 000 deaths and 373 000 hospital discharges in 1998.[8] These numbers could be an underestimation, since we recognise the high prevalence of undiagnosed cirrhosis in both non-alcoholic steatohepatitis and hepatitis C. Similar numbers have been reported from Europe, and numbers are even higher in most Asian and African countries where chronic viral hepatitis B or C are common. Since compensated cirrhosis often goes undetected for extended periods, a reasonable estimate is that up to 1% of populations could have histological cirrhosis.

Causes of cirrhosis

Causes of cirrhosis can usually be identified by the patient's history combined with serological and histological investigation (table 1).[9–17] Alcoholic liver disease and hepatitis C are the most common causes in developed countries, whereas hepatitis B is the prevailing cause in most parts of Asia and sub-Saharan Africa. After the identification of hepatitis C virus in 1989 and of non-alcoholic steatohepatitis in obese patients with diabetes, the diagnosis of cirrhosis without an apparent cause (cryptogenic cirrhosis) is rarely made. The causes of cirrhosis can predict complications and direct treatment decisions. Knowledge of the cause also allows the discussion of preventive measures, for example, with family members of patients with alcoholic cirrhosis or chronic viral hepatitis, and consideration of (genetic) testing and preventive advice for relatives of patients with genetic diseases, such as haemochromatosis or Wilson's disease.

Epidemiological studies have identified a number of factors that contribute to the risk of developing cirrhosis. Regular (moderate) alcohol consumption, age older than 50 years, and male gender are examples that increase cirrhosis risk[18–20] in chronic hepatitis C infection, and older age, obesity, insulin resistance or type 2 diabetes, hypertension, and hyperlipidaemia (all features of the metabolic syndrome) in non-alcoholic steatohepatitis.[21,22]

Clinical presentation

Cirrhosis is often indolent, asymptomatic, and unsuspected until complications of liver disease are present. Many of these patients never come to clinical attention, and previously undiagnosed cirrhosis is often found at autopsy.[23] Diagnosis of asymptomatic cirrhosis is usually made when incidental screening tests such as liver transaminases or radiological findings suggest liver disease, and patients undergo further assessment and liver biopsy (table 2).[24–28] The recognition that 20% of patients with hepatitis C and as many as 10% of patients with non-alcoholic steatohepatitis could progress to cirrhosis has led to the common use of biopsy in these high-risk groups before clinical signs of cirrhosis develop. However, initial clinical presentation of patients with decompensated cirrhosis is still common and is characterised by the presence of striking and life-threatening complications, such as variceal haemorrhage, ascites, spontaneous bacterial peritonitis, or hepatic encephalopathy.

Imaging of cirrhosis

Ultrasonography, CT, and MRI are not sensitive enough to detect cirrhosis, and final diagnosis still relies on histology. However, their specificity is high if the cause is obvious, and imaging reveals an inhomogeous hepatic texture or surface, rarefied hepatic central vein, an enlarged caudate lobe, splenomegaly, or collateral

	Description	Cause
Jaundice[1–3]	Yellow discoloration of skin, cornea, and mucous membranes	Compromised hepatocyte excretory function, occurs when serum bilirubin >20 mg/L
Spider angiomata[9,10]	Central arteriole with tiny radiating vessels, mainly on trunk and face	Raised oestradiol, decreased oestradiol degradation in liver
Nodular liver[2]	Irregular, hard surface on palpation	Fibrosis, irregular regeneration
Splenomegaly[2]	Enlarged on palpation or in ultrasound	Portal hypertension, splenic congestion
Ascites[1–3,11]	Proteinaceous fluid in abdominal cavity, clinically detected when ≥1·5 L	Portal hypertension
Caput medusae[2]	Prominent veins radiating from umbilicus	Portal hypertension, reopening of umbilical vein that shunts blood from portal vein
Cruveilhier-Baumgarten syndrome[12]	Epigastric vascular murmur	Shunts from portal vein to umbilical vein branches, can be present without Caput medusae
Palmar erythema[1–3]	Erythema sparing central portion of the palm	Increased oestradiol, decreased oestradiol degradation in liver
White nails[13]	Horizontal white bands or proximal white nail plate	Hypoalbuminaemia
Hypertrophic osteoarthropathy/ finger clubbing[14]	Painful proliferative osteoarthropathy of long bones	Hypoxaemia due to right-to-left shunting, portopulmonary hypertension
Dupuytren's contracture[15]	Fibrosis and contraction of palmar fascia	Enhanced oxidative stress, increased inosine (alcohol exposure or diabetes)
Gynecomastia, loss of male hair pattern[16]	Benign proliferation of glandular male breast tissue	Enhanced conversion of androstenedione to oestrone and oestradiol, reduced oestradiol degradation in liver
Hypogonadism[1–3]	Mainly in alcoholic cirrhosis and haemochromatosis	Direct toxic effect of alcohol or iron
Flapping tremor (asterixis)[1–3]	Asynchronous flapping motions of dorsiflexed hands	Hepatic encephalopathy, disinhibition of motor neurons
Foetor hepaticus[17]	Sweet, pungent smell	Volatile dimethylsulfide, especially in portosystemic shunting and liver failure
Anorexia, fatigue, weight loss, muscle wasting[1–3]	Occurs in >50% of patients with cirrhosis	Catabolic metabolism by diseased liver, secondary to anorexia
Type 2 diabetes[1–3]	Occurs in 15–30% of patients with cirrhosis	Disturbed glucose use or decreased insulin removal by the liver

Data from references 1–3, and 15 if not specified otherwise. *Usually absent in compensated cirrhosis; some findings only occur in a few cases.

Table 1: **Clinical features of cirrhosis***

	Description	Cause
AST, ALT	Often normal or moderately raised	Leakage from damaged hepatocytes; AST-to-ALT ratio often >1, especially in alcoholic cirrhosis (relative vitamin B6 deficiency)
ALP	Increased by less than three-fold, apart from PBC and PSC	Cholestasis
γ-GT	More specific for liver than ALP, high concentrations in active alcoholics	Cholestasis
Bilirubin	Raised later than γ-GT and ALP, important predictor of mortality	Cholestasis, decreased hepatocyte and renal excretory function (exacerbated by systemic inflammation)
Albumin	Decreased in advanced cirrhosis	Decreased hepatic production, sequestration into ascites and interstitium (exacerbated in systemic inflammation); DD: malnutrition, protein losing enteropathy
Prothrombin time	Decreased in advanced cirrhosis	Decreased hepatic production of factor V/VII (while thrombin production is maintained); DD: vitamin K deficiency (eg, due to mechanical biliary obstruction)
Immunoglobulins	Increased (mainly IgG)	Shunting of portal venous blood carrying (intestinal) antigens to lymph tissues with resultant stimulation of plasma cells[26]
Sodium imbalance	Hyponatraemia	Inability to excrete free water via kidneys due to increased activity of antidiuretic hormone (vasopressin 2 receptor effect)[27]
Anaemia	Macrocytic, normocytic, or microcytic anaemia	Folate deficiency, hypersplenism, direct toxicity (alcohol), gastrointestinal blood loss (eg, via oesophageal varices)
Thrombocytes and leucocytes	Thrombocytopenia (leucopenia)	Hypersplenism, dysfibronogenemia, reduced hepatic thrombopoietin production[28]

Data from references 1–3, and 25 if not specified otherwise. AST=aspartate aminotransferase. ALT=alanine aminotransferase. ALP=alkaline phosphatase. DD=differential diagnosis. γ-GT=γ-glutamyl transpeptidase. PBC=primary biliary cirrhosis. PSC=primary sclerosing cholangitis.

Table 2: **Laboratory tests and findings in cirrhosis**

veins.[29–32] However, other causes such as portal-vein thrombosis, parasitic diseases, or haematological cancers need to be excluded, and normal radiographic findings do not exclude compensated cirrhosis. The primary role of radiography is for the detection and quantitation of complications of cirrhosis—ie, ascites, hepatocellular carcinoma, and hepatic vein or portal vein thrombosis.

Ultrasonography provides important information about hepatic architecture, is inexpensive, and is widely available. Nodularity and increased echogenicity of the liver are often found in cirrhosis but are also present in steatosis.[30,31] Atrophy of the right lobe and hypertrophy of the left and especially caudate lobes are typical signs. However, the width of the caudate relative to the right lobe is a poor predictor of cirrhosis.[32] Ultrasonography and doppler ultrasonography of portal-vein and central-vein diameters and velocities are useful screening tests for portal hypertension and vessel patency. Contrast ultrasonography examines the appearance of echogenic microbubbles in the hepatic vein. Their appearance after antecubital injection is correlated inversely with fibrosis.[33,34] Ultrasonography is the first imaging method for suspected hepatocellular carcinoma, but its sensitivity and specificity to detect hepatocellular cancer is lower than that of CT or MRI,[35] and the malignant potential of nodular lesions should be confirmed by helical CT or MRI. When there is a high degree of suspicion that a malignancy is present, (eg, in patients with α-fetoprotein >200 μg/L) or as part of pretransplantation assessment, the helical CT or MRI should be used, even in the absence of ultrasonographic lesions. Contrast ultrasonography, harmonic imaging, and power doppler improve detection of hepatoceullar carcinoma via sensitive visualisation of abnormal vessels but are not yet generally available.[36]

Conventional CT and MRI can be used to define the severity of cirrhosis—eg, by determining spleen size, ascites, and vascular collaterals[37]—but helical CT and MRI with contrast are preferred if hepatocellular carcinoma or vascular lesions are suspected.[38] In a comparison, MRI was found to be better than helical CT at detecting small hepatocellular cancers (1–2 cm size).[39] MRI has also been shown to be effective in determining hepatic iron and fat content in haemochromatosis and liver steatosis, respectively.[40,41]

A promising new technique assesses liver stiffness based on the velocity of an elastic wave via an intercostally placed transmitter. Shear wave velocity is determined by pulse ultrasound and correlates with liver stiffness—ie, fibrosis. The examination is limited by morbid obesity, ascites, and small intercostal spaces. In a study of 327 patients with hepatitis C, histological cirrhosis was differentiated from milder stages of fibrosis with a receiver-operating characteristics (ROC) curve of 0·97, which is considered an almost ideal test.[42] Elasticity scans have the ability to sample 1/500 of the liver and represent a useful, non-invasive test for diagnosis of or exclusion of cirrhosis.

Liver biopsy

Biopsy is considered the gold standard for diagnosis of cirrhosis, and sequential histological grading of

	Specific physical associations	Diagnostic (laboratory) variables	Value of liver biopsy (identifiable features)
HBV	Arthritis	HBsAg, HBeAg, HBc-antibodies, HBV DNA	+
HCV	Cryoglobulinaemia	HCV antibodies, HBV RNA	+
Viral hepatitis D	..	HBsAg, HDV antibodies, HDV RNA	++ (HDAg)
Alcoholic	..	AST:ALT ratio ≥2, increased CDT and γ–GT	++ (Mallory bodies, steatosis, granulocytes >hepatocyte ballooning)
Non-alcoholic steatohepatitis	Overweight/obesity, metabolic syndrome, type 2 diabetes	Uric acid, fasting glucose/insulin/triglycerides	++ (Mallory bodies, steatosis, hepatocyte ballooning>granulocytes)
Autoimmune	..	Autoantibodies (ANA, LKM antibodies, SLA antibodies), increased γ-globulins	+++ (bridging necrosis)
Primary biliary cirrhosis	Sicca syndrome, xanthelasma	AMA; increased ALP, γGT, and cholesterol	++ (cholangitis, paucity of bile ducts, granuloma, ductopenia)
Primary sclerosing cholangitis	Ulcerative colitis (90%)	pANCA antibodies (70%), increased ALP and γGT, imaging: beaded intra-hepatic and extra-hepatic bile ducts	+++ (concentric peribile ductular fibrosis, ductopenia)
Haemochromatosis	Arthritis, myocarditis, diabetes	Fasting transferrin saturation >60% (men), >50% (women); increased ferritin, HFE mutation	++ (periportal iron-loaded hepatocytes, quantification of liver iron)
Wilson's disease	Neurological	Increased oeruloplasmin, and copper in 24 h urine; slit-lamp: corneal copper deposits	+++ (quantification of liver copper)
α1-antitrypsin	Pulmonary fibrosis	Reduced α1-antitrypsin; α1-antitrypsin subtyping	+++ (α1-antitrypsin-loaded hepatocytes)
Congenital disease	..	..	+++ (eg, bile ductular plate malformations)

HBcAg=hepatitis B core antigen. HBe=hepatitis B envelope antigen. HBsAg=hepatitis B surface antigen. HBV=viral hepatitis B. HCV=viral hepatitis C. HDAg=hepatitis D antigen. HDV=viral hepatitis D. AST=aspartate aminotransferase. ALT=alanine aminotransferase. AMA=antimitochondrial antibodies. ANA=anti-nuclear antibodies. CDT=carbohydrate-deficient transferrin. γ-GT=γ-glutamyl transpeptidase. HFE=haemochromatosis C282Y mutation. LKM=liver kidney membrane. SLA=soluble liver antigen. pANCA=perinuclear neutrophil cytoplasmic antigen.

Table 3: **Diagnostic tests in chronic liver disease, according to cause**

inflammation and staging of fibrosis can assess risk of progression. Furthermore, biopsy is important for establishing the cause of cirrhosis in up to 20% of patients with previous unknown cause (table 3). However, biopsy is prone to considerable sampling variability in all liver diseases.[43–46] The staging of fibrosis in hepatitis C by use of the METAVIR system (which is simple and uses only five stages, with stage four indicating cirrhosis) showed that a third of scores differed by at least one stage when a biopsy sample from the left liver lobe was compared with that from the right lobe, with similar results for inflammation grading.[45] In hepatitis C, correct staging was only achieved for 65% and 75% of cases when biopsy samples were 15 mm and 25 mm in length, respectively,[44] whereas only 16% of samples in practice reach 25 mm in length. Despite these shortcomings, biopsies are still needed to confirm cirrhosis in patients with compensated liver function and to suggest possible causes. Biopsy confirmation of cirrhosis is not necessary if clear signs of cirrhosis—such as ascites, coagulopathy, and a shrunken nodular-appearing liver—are present.

A liver biopsy sample is obtained by either a (radiographically-guided) percutaneous, transjugular, or laparoscopical route. An increased risk of bleeding after biopsy has been seen with large-diameter needles (<1·4 mm). In suspected cirrhosis, cutting is preferred over suction needles, to prevent tissue fragmentation.[47] 2–3% of patients need hospital care for management of complications, of which pain or hypotension are the predominant causes. 60% of complications occur within 2 h after biopsy, and 96% within 24 h. Probability of mortality, mainly due to severe bleeding, is 1 in 10 000 to 12 000, and is probably higher in cirrhosis.[47] Blood products should be given if the platelet count is less than 70 000 per μL, if prothrombin time is prolonged by more than 4 seconds, or if a transjugular or laparoscopic approach is chosen. Aspirin and other antiplatelet drugs should be stopped at least 1 week before biopsy.

Natural history and prognosis

The natural history of cirrhosis depends on both the cause and treatment of the underlying cause. Yearly rates of decompensation are 4% for viral hepatitis C and 10% for viral hepatitis B, and incidence of hepatocellular carcinoma is 2–7% per year. Decompensation in alcoholic cirrhosis with continued alcohol use is even more rapid and often associated with alcoholic hepatitis on a background of cirrhosis. Once decompensation has occurred in all types of liver disease, mortality without transplantation is as high as 85% over 5 years.

Many studies have attempted to develop a classification system that can both characterise the degree of liver injury and predict the prognosis of patients with cirrhosis on the basis of clinical and laboratory variables. Because of its low simplicity and fairly good predictive value, the Child-Pugh-Turcotte (CPT) classification is

widely used (table 4).[48] 1-year survival rates for patients with CPT class A, B, and C cirrhosis are 100%, 80%, and 45%, respectively.[49] CPT class predicts the development of complications, such as variceal haemorrhage and the response of patients to surgical interventions.[50] Because of the shortage of donated livers, the Model for End Stage Liver Disease (MELD) has recently been developed to provide a more accurate prediction of short-term mortality.[51] MELD best predicts 3-month survival of cirrhotic patients, irrespective of cause. The model is based on creatinine, bilirubin, and international normalised ratio (INR), but does not include features of portal hypertension, such as ascites. It gives priority to patients who are most likely to die without a liver transplant, such as those with hepatorenal failure. In the USA, replacing the previous system, which gave great weight to time spent on the waiting list, with MELD has reduced mortality on the waiting list without change in post-transplant outcome. The system is currently considered for further refinement, such as additional points given to patients with hepatocellular carcinoma and hyponatraemia lower than 130 mEq/mL.[52] CPT and MELD scores can vary greatly if single variables are modified by medical treatment, such as substitution of albumin, removal of ascites, or diuretic treatment (which can increase serum creatinine). Here, an increasing MELD score over time is a better predictor of cirrhosis severity and progression than is CPT.[53]

Treatment and reversibility of cirrhosis

Elimination of the triggers leading to cirrhosis will probably delay progression to a higher CPT class and reduce the occurrence of hepatocellular carcinoma. Reports have shown that causal treatment could even reverse cirrhosis, although in some reports the effect of sampling variability cannot be excluded. Patients with alcoholic cirrhosis should not continue alcohol consumption because it drives hepatitis, which favours hepatic fibrogenesis and decompensation.[54–56] Liver function often worsens in the first 2–3 weeks of withdrawal, since alcohol has an immunosuppressive effect.[57]

	1 point	2 points	3 points
Encephalopathy	Absent	Medically controlled	Poorly controlled
Ascites	Absent	Controlled medically	Poorly controlled
Bilirubin (mg/L)	<20	20–30	>30
Albumin (g/L)	<35	28–35	<28
INR	<1·7	1·7–2·2	>2·2

CPTA (5–6 points), CPTB (7–9 points), and CPTC (10–15 points) predict a life expectancy of 15–20, 4–14, and 1–3 years, respectively, and a perioperative mortality (abdominal surgery) of 10%, 30%, and 80%, respectively. INR=international normalised ratio.

Table 4: **Child Pugh Turcotte (CPT) classification**

Patients with compensated cirrhosis and with replicating hepatitis C virus benefit from interferon-based antiviral treatment. Viral eradication and a consequently lowered risk of hepatic decompensation and hepatocellular carcinoma can be achieved in up to 40% of patients with genotype 1 and in 70% of patients with genotypes 2 or 3.[58] In a meta-analysis,[59] 75 of 153 patients with biopsy-proven cirrhosis showed reversal of cirrhosis on biopsy after successful treatment, but results need confirmation in view of biopsy sampling variability. Large prospective trials (HALT-C [hepatitis C long-term antiviral treatment against cirrhosis], EPIC-3 [evaluation of PegIntron in control of hepatitis C cirrhosis], and COPILOT [colchicine *vs* PegIntron long-term trial])[58] are investigating how far maintenance interferon for 3–4 years can prevent hepatic decompensation or hepatocellular carcinoma in patients with stage 3–4 fibrosis who have not responded to interferon-ribavirin treatment.

Long-term treatment with oral nucleoside and nucleotide inhibitors of hepatitis B virus DNA polymerase might not only retard or reverse cirrhosis,

	Prevention	Treatment
Variceal bleeding[72–75]	Non-selective β blockers* Variceal band ligation	Acute: Resuscitation Vasocontrictors† Sclerotherapy Band ligation TIPS Surgical shunts Chronic: Variceal obliteration TIPS Surgical shunts
Ascites[72,76]	Low sodium diet	Low sodium diet Diuretics Large volume paracentesis TIPSS (LeVeen/Denver shunts)
Renal failure[77]	Avoid hypovolaemia	Discontinue diuretics Rehydration Albumin infusion Hepatorenal syndrome: add terlipressin or midodrine (noradrenaline) and somatostatin (octreotide)
Encephalopathy[78]	Avoid precipitants	Treat precipitating factors: Infection Bleeding Electrolyte imbalance Sedatives High protein intake Lactulose Neomycin, metronidazole, rifaximin
Spontaneous bacterial peritonitis[72]	Treat ascites	Early diagnosic paracentesis: >250 neutrophils per mL, intravenous antibiotics (plus albumin) Secondary prophlaxis with oral antibiotics such as levofloxacin

TIPSS=transjugular intrahepatic portosystemic shunt. *Nadolol, propranolol. †Vasopressin, octreotide/somatostatin, terlipressin.

Table 5: **Prevention and treatment for complications of cirrhosis**

but also have been shown to prevent complications of end-stage liver disease. In a 3-year study of lamivudine for hepatitis B, follow-up liver biopsies indicated reversal of cirrhosis in eight (73%) of 11 patients.[60] Additionally, 436 of 651 patients with cirrhosis from hepatitis B given lamivudine for a mean of 32 months showed a more than 50% reduction of hard clinical endpoints (hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease).[61] In patients with cirrhosis and replicating hepatitis B (>10^5 copies per mL), lamivudine treatment often resulted in clinical improvement, even after decompensation.[62–64] The high rate of lamivudine resistance, which reaches 56% and 70% after 3 and 4 years of treatment, respectively, is now of less concern, since equally tolerable alternatives such as adefovir,[65] entecavir,[66] or telbivudine,[67] or their combinations induce lower viral resistance and a different mutational profile. In one large study, adefovir was successfully used in patients with lamivudine resistance before transplantation, leading to suppression of viral replication of hepatitis B to undetectable levels in 76% of patients with either a stabilisation or improvement in CTP score and a 90% survival.[68]

The data for reversibility and stabilisation of other causes of cirrhosis are less well established. Cohort studies have shown that some patients with cirrhosis who also had autoimmune hepatitis showed regression after long-term treatment with corticosteroids,[69,70] and venesection of patients with hereditary haemochromatosis could reduce the development of complications of portal hypertension.[71]

Complications of cirrhosis

Major advances have been made in recent years to both prevent and treat the common complications of cirrhosis such as variceal bleeding, ascites, spontaneous bacterial peritonitis, and encephalopathy (table 5).[72–78] However, bacterial infections are common, especially in decompensated cirrhosis, which exacerbates hepatic dysfunction, encephalopathy, and portal hypertension, and underlines the need for vigilance and rigorous antibiotic treatment. Enhanced bacterial translocation from the intestine, compromised immune function, and excessive proinflammatory cytokine release have been implicated in the pathogenesis of the cirrhosis-associated systemic inflammatory syndrome.[79] An example is the failure to control oesophageal variceal bleeding with associated bacterial infection.[80]

Clinicians should realise that once complications have developed, suitable patients should be referred to liver centres that specialise in both the care of patients with end-stage liver disease and liver transplantation. Circulatory and cardiac abnormalities in cirrhosis should be noted, which can preclude transplantation eligibility. Hepatopulmonary syndrome, which occurs in 15–20% of patients with cirrhosis, is due to overproduction of nitric oxide and overexpression of the endothelin B receptor, with consequent pulmonary arteriolar vasodilation, shunting, and hypoxaemia.[81,82] The disorder is largely reversible after transplantation. Portopulmonary hypertension is rare, but occurs in up to 16–20% of patients with refractory ascites. It is probably caused by an excess of pulmonary arteriolar vasoconstrictors and profibrogenic factors such as transforming growth factor (TGF)-β1.[83] The condition is deemed irreversible and pulmonary artery pressures of more than 40 mm Hg

***Panel 1:* Risk factors for hepatocellular carcinoma**

- Cirrhosis
- Decompensated cirrhosis
- Viral hepatitis B and C
- Non-alcoholic steatohepatitis
- Type 2 diabetes
- Aflatoxin exposure
- Coinfection with multiple viruses; viral hepatitis B, viral hepatitis C, and HIV (risk 2–6-fold)
- Increasing age
- Male sex
- Positive family history of hepatocellular carcinoma
- Associated secondary alcohol abuse (risk 2–4-fold) or non-alcoholic steatohepatitis as cofactor

***Panel 2:* Indications and contraindications for orthotopic liver transplantation**

Indications

Advanced chronic liver failure

- CPT score >7
- Qualifying MELD score for organ allocation

Acute liver failure

- Drug induced fulminat viral hepatitis

General

- No alternative form of treatment
- No absolute contraindications
- Willingness to comply with follow-up care
- Ability to provide for costs of liver transplantation

Contraindications

Relative

- HIV seropositivity
- Methadone dependence
- Stage 3 hepatocellular carcinoma*

Absolute

- Extrahepatic malignant disease
- AIDS
- Cholangiocarcinoma
- Severe, uncontrolled systemic infection
- Multiorgan failure
- Advanced cardiopulmonary disease
- Active substance abuse

*Not fulfilling the Milan criteria (see text).

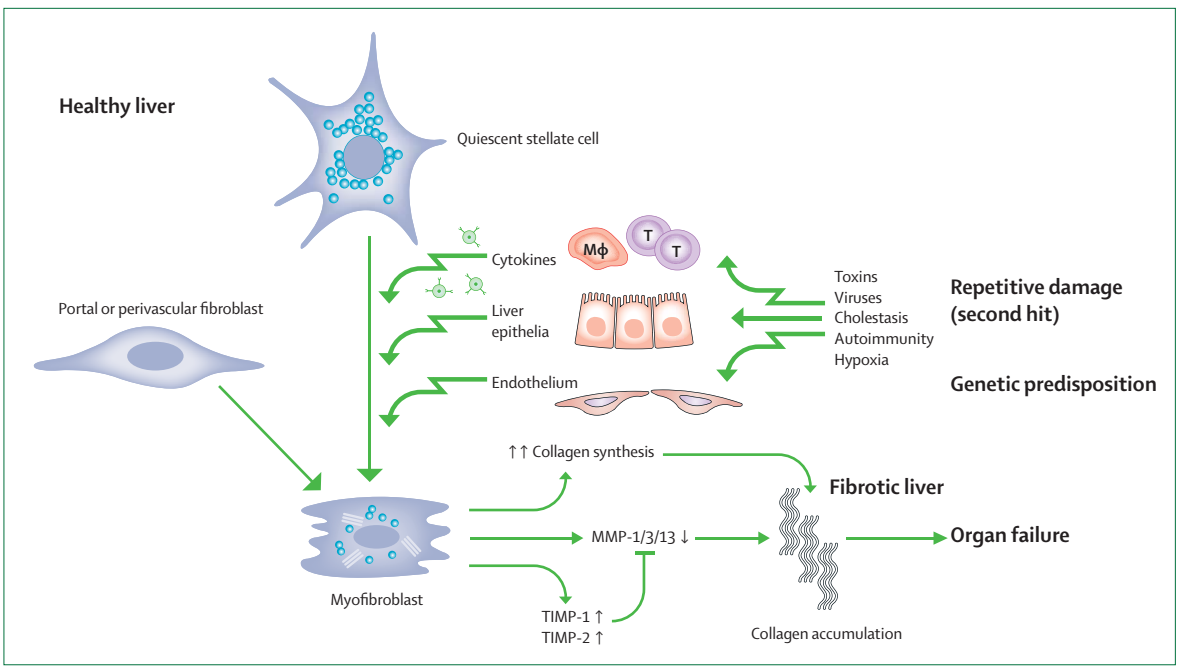

Figure 2: **Initiation and maintenance of fibrogenesis**
With continuous injury, mainly to hepatocytes or bile-duct epithelia, or mechanical stress, the typically quiescent hepatic stellate cells and portal or perivenular fibroblasts undergo activation and transdifferentiation to myofibroblasts. These myofibroblasts produce excessive amounts of collagens, downregulate their production of matrix metalloproteinases (MMPs), and show an enhanced expression of the physiological inhibitors of the MMPs (TIMP1 and TIMP2). TIMP1 can also promote myofibroblast proliferation and inhibit their apoptosis.

preclude liver transplantation.[84] Cirrhotic cardiomyopathy is characterised by a blunted stress response of the heart, combined with hypertrophy.[85] Severe forms increase postoperative mortality and preclude transplantation.

Hepatocellular carcinoma

Hepatocellular carcinoma is one of the commonest solid organ tumours worldwide, and cirrhosis is a major risk factor for progression, among others (panel 1).[86–88] Its pathogenesis seems to arise from the development of regenerative nodules with small-cell dysplasia through to invasive hepatocellular carcinoma. Mortality of hepatocellular carcinoma associated with cirrhosis is rising in most developed countries, whereas mortality from cirrhosis not related to hepatocellular carcinoma is decreasing.[89] The highest incidence of hepatocellular carcinoma results from cirrhosis due to hepatitis C, especially in Japan when compared with the USA and Europe, followed by hereditary haemochromatosis (5-year cumulative incidence 17–30%). In cirrhosis due to hepatitis B, which is the major cause of deaths related to hepatocellular carcinoma worldwide, the 5-year cumulative occurrence of hepatocellular carcinoma is 15% in highly endemic areas and 10% in the USA and Europe. 5-year occurrence is lower in alcoholic patients with cirrhosis, or in patients with biliary cirrhosis (8% and 4%, respectively). Hepatocellular carcinoma is increasing in the USA, where its incidence had risen from 1·8 to 2·5 per 100 000 people in one decade, mainly attributable to hepatitis C viral infection.[90]

Screening for hepatocellular carcinoma is one of the most important tasks in the following of patients with cirrhosis. Current American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) guidelines recommend at least one screening per year for hepatocellular carcinoma in patients with cirrhosis using imaging with ultrasonography, triphasic CT, or gadolinium-enhanced MRI.[86–88] Serum α-fetoprotein, which was an integral component of previous screening algorithms, is no longer recommended because of its poor sensitivity and specificity. Once hepatocellular carcinoma is detected, many treatments are available that depend on tumour size, tumour number, and local expertise. In patients

Panel 3: **Desired characteristics of non-invasive markers of liver fibrosis**

- Be liver-specific
- Levels not affected by alterations in liver, renal, or reticuloendothelial function
- Exact measurement of one or more of following processes:
  - Stage of fibrosis
  - Activity of matrix deposition (fibrogenesis)
  - Activity of matrix removal (fibrolysis)
- Easy and reproducible performance characteristics
- Able to predict risk of disease progression or regression

without cirrhosis, surgical resection is an option and can be curative. However, most patients with cirrhosis will not tolerate liver resection or have microscopic satellite lesions, and the best option for cure is liver transplantation. The Milan criteria, which are used as a guideline in most liver centres worldwide, have suggested that the mortality and recurrence of hepatocellular carcinoma is acceptable if liver transplantation is done for either a single tumour of less than 5 cm in diameter, or no more than three tumours with the largest being less than 3 cm in diameter. Alternative treatments for patients who do not meet the criteria for surgical resection or transplantation are radiofrequency ablation, chemoembolisation, alcohol ablation, and cyberknife radiotherapy.[86–88] These modalities can also serve as a bridge to transplantation. Their selection depends on local expertise, and randomised trials suggesting that they improve long-term survival are scarce.

Liver transplantation

The ultimate treatment for cirrhosis and end-stage liver disease is liver transplantation (panel 2). Most recent survival data from the United Network of Organ Sharing (UNOS) study[91] indicates survival rates of 83%, 70%, and 61% at 1 year, 5 years, and 8 years, respectively. Survival is best in patients who are at home at the time of transplantation compared with those who are in the hospital or intensive-care unit. Advances in liver transplantation have been the improvement in immunosuppressive regimens so that allograft loss from rejection is now rare.[92,93] However, recurrent disease in the transplant (especially viral hepatitis C) and long-term consequences of immunosuppressive drugs (eg, hypertension, hyperlipidaemia, and renal disease) must be closely monitored after transplantation.

Recent advances and future directions

Molecular pathology of hepatic fibrosis and cirrhosis

The scar tissue in cirrhosis is composed of a complex assembly of different extracellular matrix molecules (ECM), consisting of: the fibril-forming interstitial collagens type I and III; basement membrane collagen type IV; non-collagenous glycoproteins such as fibronectin and laminin; elastic fibres; and glycosaminoglycans and proteoglycans, among others.[94] Toxins, viruses, cholestasis, or hypoxia can trigger a wound healing reaction termed fibrogenesis—ie, the excess synthesis and deposition of ECM. Initially, fibrogenesis is counterbalanced by removal of excess ECM by proteolytic enzymes, such as specific matrix metalloproteinases (MMPs).[95] Chronic damage usually favours fibrogenesis over fibrolysis, with an upregulation of tissue inhibitors of MMPs (TIMPs).[95] The major hepatic ECM-producing cells are myofibroblasts that either derive from activated hepatic stellate cells or perivascular fibroblasts.[96–98] Myofibroblast activation is mainly driven via fibrogenic cytokines and growth factors that are released by activated macrophages

	N	Cause	AUROC (SD)	% classified
Fibrotest*[113]	352	HCV	0·76 (0·03)	46%
Fibrotest[114]	209	HBV	0·78 (0·04)	..
Forns index†[115]	476	HCV	0·78	49%
APRI‡[116]	192	HCV	0·80 (0·06)	51%
APRI[117]	484	HCV	0·74	57%
HA, TIMP-1, α2M[120]	696	HCV	0·831	..
HA, PIIINP, TIMP-1, age[121]	921	All liver diseases	0·804 (0·02)	..
HA, albumin, AST[122]	137	HCV/HIV	0·87	..
Comparisons				
APRI *vs* Fibrotest[118]	323	HCV	0·74 (0·03) 0·83 (0·02)	..
APRI *vs* AST:ALT ratio[119]	239	HCV	0·773 0·820	..
Fibroscan plus Fibrotest[127]	183	HCV	0·88	..

Performance of tests is better for differentiating F3–4 (4=cirrhosis) from F0–1 than vice versa. AUROC=area under receiver operator curve. HBV=viral hepatitis B. HCV=viral hepatitis C. α2M=α2-macroglobulin. AST=aspartate aminotransferase. ALT=alanine aminotransferase. Matrix-derived markers: hyaluronic acid (HA), aminoterminal propeptide of procollagen III (PIIINP), tissue inhibitor of matrix metalloproteinase 1 (TIMP-1). Test combinations are: *Algorithm of bilirubin, δ-glutamyl transpeptidase (GT), δ-globulin, haptoglobin, α2-macroglobulin, age; †algorithm of g-GT, cholesterol, platelets, age; AST to platelet ratio index (APRI): AST (upper limit of normal) divided by platelets (109/ L), either ≤0·5 (for F0–1) or >1·5 (for F2–4).

Table 6: **Differentiation of fibrosis stage F0–1 from F2–4 by serum markers and Fibroscan**

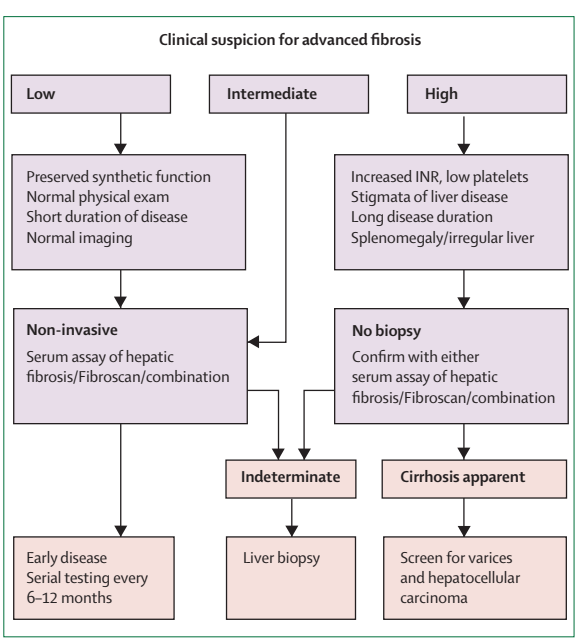

Figure 3: **Use of biomarkers for staging of liver fibrosis and diagnosis of cirrhosis**

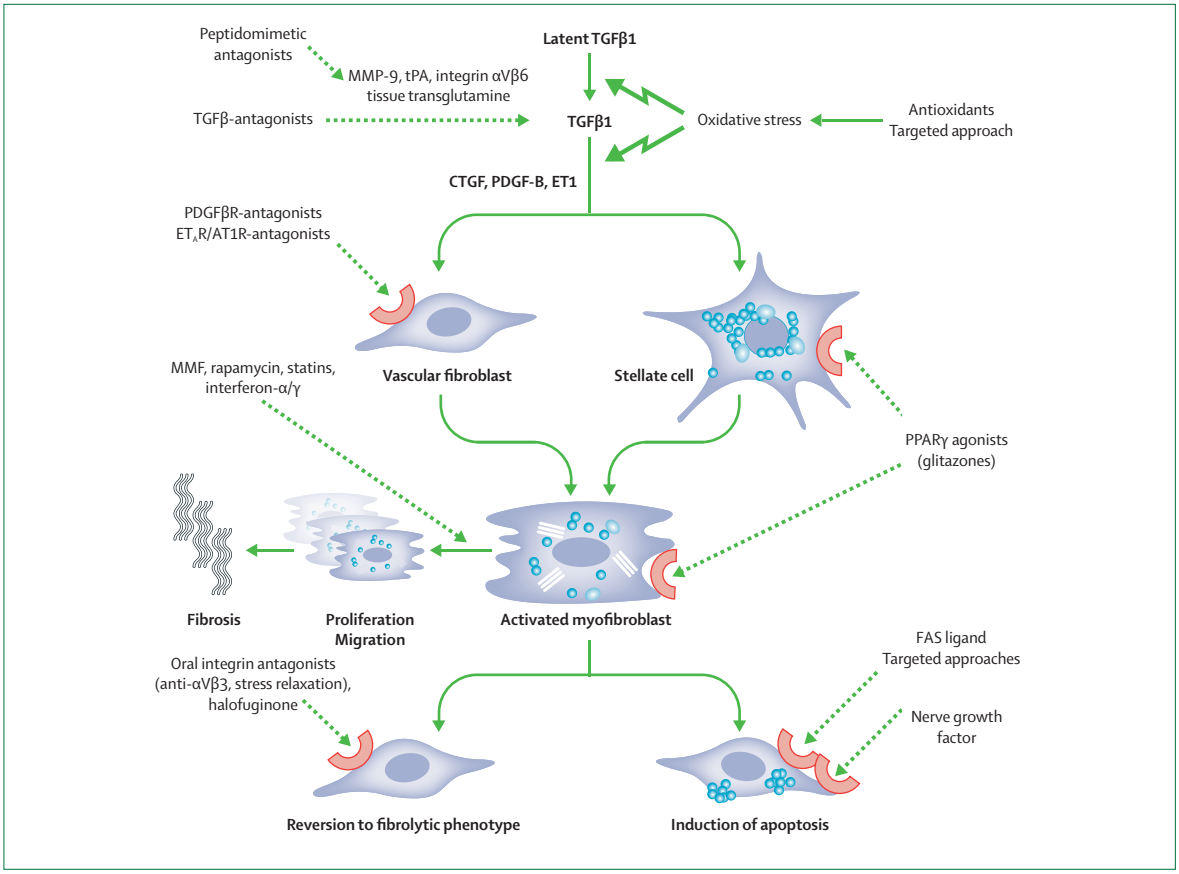

Figure 4: **Antifibrotic approaches and candidates for combination treatment**
Only approaches that target the activated myofibroblasts are shown, although there also exist antifibrotic strategies that target activated bile duct epithelia or Kupffer cells. An important principle is inhibition of TGF-β, either by blocking molecules that induce its proteolytic activation from latent TGF-β, or by its direct inhibition. However, this approach has to be targeted, since complete abrogation of TGF-β leads to cellular dedifferentiation and severe (intestinal) inflammation. AT=angiotensin. AT1R=angiotensin 1 receptor. CTGF=connective tissue growth factor. ET1=endothelin 1. ETAR=endothelin A receptor. MMF=mycophenolate mofetil. MMP=matrix metalloproteinase. PDGF=platelet-derived growth factor. tPA=tissue plasminogen activator. PPAR=peroxisome-proliferator-activated receptor.

(Kupffer cells), other inflammatory cells, and bile duct epithelia (figure 2). The most prominent profibrogenic cytokine is TGF-β, which suppresses inflammation but drives fibrogenic gene expression in these myofibroblasts.[96,98,99]

Genetic predisposition for cirrhosis

Variable rates of development of cirrhosis in individuals with similar risk factors such as hepatitis C or alcohol abuse have long been unexplained. Recently, a growing number of functional genetic polymorphisms that probably increase the risk of fibrosis progression has been described. Implicated genes encode cytokines or chemokines and their receptors,[100,101] molecules involved in fibrogenesis or fibrolysis,[102] blood coagulation,[103] antigen presentation,[104] iron uptake,[105] oxidative and antioxidative metabolism,[106] detoxification,[107] and polygenetic traits linked to the metabolic syndrome and non-alcoholic steatohepatitis. In a gene association study,[108] 1609 of 24882 single nucleotide polymorphisms (SNPs) were found to be associated with fibrosis progression in chronic hepatitis C, with the *DDX5* gene having a high positive predictive value.[108] With established extrinsic risk factors such as excess alcohol consumption, obesity, or advanced age, these SNPs will allow the establishment of risk profiles for individual patients.[109] However, most of the polymorphisms need confirmation in larger cohorts.[109]

Feasibility of pharmacological reversal of cirrhosis

The findings that even cirrhosis can regress once the fibrogenic trigger is eliminated[5,6,59,60,69–71,110] can be explained by the dynamic processes of fibrogenesis and fibrolysis even in cirrhosis.[6] Although the central role of activated hepatic stellate cells (myofibroblasts) in fibrogenesis is unchallenged, other cells contribute. Thus macrophages or Kupffer cells have been shown to retard progression in early fibrosis but promote progression in advanced fibrosis.[111] Furthermore, regression from macronodular to micronodular cirrhosis and possible cirrhosis reversal depends on the degree of ECM crosslinking, which is catalysed by enzymes such as tissue transglutaminase.[112]

The rapid progress in the understanding of molecular mechanisms leading to cirrhosis or its reversal has spawned the development of antifibrotic drugs. We can classify the therapeutic approaches to reversal of fibrosis as primary and secondary. Primary approaches focus on treatment of the underlying disease such as hepatitis B and C that have been shown to result in regression of (compensated) cirrhosis.[59,60,72] The secondary approach is to develop intrinsic antifibrotic drugs that specifically target the mechanism of fibrogenesis, irrespective of the cause of the liver disease.

The major obstacle to antifibrotic drug development has been the difficulty in defining validated endpoints for clinical trials. The combination of a slowly evolving disease (years to decades) and an established endpoint (liver biopsy) that has restricted sensitivity and substantial sampling variability is a stumbling block for study design. In particular, without short-term surrogate markers for liver fibrosis, exploratory studies are hampered by the need for large sample sizes and the high risk of failure.

Non-invasive markers of fibrogenesis and fibrolysis

Non-invasive serological markers to cross-sectionally stage liver fibrosis[113–122] have been extensively reviewed.[123–126] Although showing potential, especially for the diagnosis of cirrhosis, none meets the criteria for an ideal surrogate fibrosis marker (panel 3). A problem is the heterogeneity of liver diseases, with different stages being present in different areas of the liver, particularly between stages 1 and 3. These markers either indicate hepatic function[113–119] or turnover of ECM (table 6).[120–122] Combinations have been developed, since no single biomarker has the adequate sensitivity and specificity. Unfortunately, current ECM-derived serum markers correlate mainly with fibrosis stage, and only to a lesser degree with fibrogenesis. We regard the performance of most of these biomarkers to be similar with a diagnostic accuracy approaching 80% for the differentiation between mild fibrosis (Metavir F0–1) and moderate to severe fibrosis (F2–4). However, the performance is consistently improved at both spectrums of disease from no fibrosis to cirrhosis, and importantly, for the prediction of cirrhosis.

Hepatic elasticity measurement (Fibroscan)[42,127,128] in combination with these serum indices could yield a better prediction of histological fibrosis than could either test alone,[127] and Fibroscan has been shown to be more effective than has Fibrotest in patients with hepatitis C and persistently normal or low transaminases.[128]

Several of these tests are available for use in clinical practice, and surrogate fibrosis markers now have a clinical role (figure 3). The major focus for research is to identify new biomarkers that allow assessment of the dynamic processes of fibrogenesis and fibrolysis, in order to monitor the effect of antifibrotic treatments in patients. This goal could be achieved by serum proteomics or glycomics,[129,130] or novel imaging techniques for sensitive assessment of fibrogenesis

Panel 4: Antifibrotic drug candidates

Inhibition of profibrogenic activation of hepatic stellate cells

Cytokines/cytokine antagonists
- Recombinant interferon-α/β/γ
- TGF-β and TGF-β-signalling antagonists (TGF-β antisense oligonucleotides, TGF-β receptor blocking peptidominetics, soluble TGF-β decoy receptors)
- Inhibition of TGF-β activation: integrin αvβ6 antagonists (EMD405270)

Phosphodiesterase-inhibitors
- Pentoxifylline, phosphodiesterase-3/4-inhibitors (rolipram)*

MMP-inducers
- Halofuginone

Prostanoids
- Prostaglandin E2

Vasoactive modulators
- Endothelin-A-receptor antagonists
- Angiotensin system inhibitors (captopril, enalapril, pirindopril, losartan, irbesartan)*
- Nitric oxide donors (pyrro-nitric-oxide)

Histone deacetylase inhibitors
- Trichostatin A, MS-275

PPAR-α agonists
- Fibrates (bezafibrate, fenofibrate)

PPAR-γ agonists
- Glitazones (pioglitazone, rosiglitazone, troglitazone)*

*Plant-derived drugs (mainly antioxidants)**
- Apigenin, compound 861, FuZhengHuaYu, glycyrrhicin, inchin-ko-to (TJ135), quercetin, resveratrol, rooibus, salvia miltiorrhiza, sho-saiko-to (TJ9), silymarin

Farnesoid-X-receptor agonists
- 6-ethyl-chenodeoxycholic acid

Inhibition of migration/proliferation of hepatic stellate cells

HMG-CoA-reductase inhibitors
- Statins

Diuretics
- Aldosterone (spironolactone); sodium/hydrogen ion exchanger (cariporide)

Immunosuppressants
- Mycophenolate mofetil, rapamycin

Angiogenesis inhibitors
- VEGF-receptor 1 and 2 antagonists (PTK787)
- Integrin αvβ3 antagonists (cilengitide, EMD409915)

Other kinase inhibitors
- PDGF-β-receptor antagonists (imatinib [SU9518])

Hepatocyte maintenance/protection
- Hepatocyte growth factor
- Insulin-like growth factor I

*Drugs that are or have been used in clinical trials aiming at inhibition of disease progression. Integrin=receptor for matrix proteins or cell-adhesion molecules. MMP=matrix metalloproteinase. PDGF=platelet-derived growth factor. PPAR=peroxosome-proliferator-activated receptor. VEGF=vascular-endothelial growth factor. HMG-CoA=hydroxymethyl-glutaryl-coenzyme A.

representing the whole liver. Such techniques could be based on CT or MRI with the use of contrast media that target activated hepatic stellate cells. Their validation probably needs parallel analysis of the liver transcriptome of patients with slow or rapid fibrosis progression,[131] an approach that needs invasive sampling of liver tissue.

Pharmacological and cellular reversal of hepatic fibrosis and cirrhosis

Many drugs with proven direct and indirect antifibrotic effects in experimental animals would merit clinical testing,[98,132–135] and efficient reversal treatments probably need antifibrotic drug combinations (figure 4). Panel 4 provides examples of drugs that have shown convincing antifibrotic activity on hepatic stellate cells in vitro, or more importantly, in suitable animal models of liver fibrosis or even in patients in vivo.[98,132–135] Most of these drugs suppress hepatic stellate cell activation directly, others prevent hepatocyte damage or loss, or halt proliferation of bile duct epithelial cells that, via release of profibrogenic factors, drive fibrogenesis. Drug effects can vary greatly between lobular and biliary fibrosis, which makes their preclinical testing in suitable animal models of lobular and biliary fibrosis obligatory. Once an antifibrotic effect has been proven in human beings (which largely depends on the development of better non-invasive markers or imaging of fibrosis progression or regression), these agents are likely to be used as combinations, either for long-term or interval therapy. Many potential antifibrotic drugs possess a reasonable safety profile, whereas their long-term safety in patients with cirrhosis has to be proven.

To achieve quick restitution of the functional parenchymal mass combined with reversal of cirrhosis, the combination of antifibrotic treatment and hepatocyte renewal is attractive.[136–138] Thus, hepatocyte transplantation has improved liver function[139,140] and ameliorated or even reversed advanced fibrosis.[141,142] Hepatocyte engraftment was increased by oxidative preconditioning and activation of hepatic stellate cells,[143,144] and infusion of hepatocyte growth factor (a potent hepatocyte mitogen) improved liver function.[145] The isolation and in-vitro expansion of hepatocyte stem cells or progenitor cells for cell transplantation could hold promise for an unlimited donor pool.[146,147] Reports that infusion of bone-marrow stem cells replenished hepatocytes, either by hepatocytic trans-differentiation,[148] fusion with hepatocytes,[149,150] or indirectly by hepatotrophic growth factors released from stem cells engrafted in the hepatic vasculature[151] sparked much enthusiasm. However, efficiency of stem or progenitor cell engraftment is generally low[152] and the manipulations currently needed to allow for sufficient engraftment in human beings would incur great risks for patients with cirrhosis and liver failure. Much refinement is needed before these techniques can be applied to patients. Similarly, the finding that genetic restitution of telomerase, an enzyme that abrogates cellular ageing by preventing chromosomal telomere shortening, can accelerate hepatic regeneration and ameliorate experimental liver fibrosis has evoked much interest.[153] However, increased telomerase activity also favours hepatocarcinogenesis, which dampens the enthusiasm for this approach.[154]

Conclusions

Many advances have occurred in the clinical care of patients with cirrhosis and the complications of end-stage liver disease. Most of these treatments have focused on the underlying cause of cirrhosis and management of complications of portal hypertension. Research in the next 10 years could focus on the primary prevention and treatment of cirrhosis, such as the use of non-invasive tests to screen for earlier stages of fibrosis and to monitor antifibrotic drug effects, and pharmacological targeting of fibrogenesis pathways. Stem-cell or hepatocyte transplantation aiming at reconstitution of liver function could become a clinical reality. Continued basic and clinical research is crucial to finally remove cirrhosis as an irreversible condition and a major contributor to morbidity and mortality in our patients.

Conflict of interest statement

We declare that we have no conflict of interest.

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