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MANAGEMENT OF CIRRHOTIC PATIENT (A CARDENAS AND P TANDON, SECTION EDITORS)

Cirrhosis and Autoimmune Liver Disease

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Abstract

Purpose of Review Autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) constitute the most frequently observed forms of autoimmune liver diseases. Each of these autoimmune liver diseases might present with cirrhosis at diagnosis, and a significant proportion of patients develop cirrhosis during follow-up. This manuscript provides a review that addresses how to monitor and manage patients with cirrhosis secondary to autoimmune liver diseases.

Recent Findings For patients with PBC, the farnesoid X receptor (FXR) agonist, obeticholic acid (OCA), is the first approved drug since ursodeoxycholic acid (UDCA) and is licensed for non-responders to or those intolerant of UDCA. Bezafibrate has been shown to be effective in non-responders to UDCA, but is not licensed for this clinical indication at present. For patients with AIH, rituximab, a monoclonal antibody against the protein CD20 is a potential option for patients with suboptimal response to corticosteroids. New treatment options are currently being investigated for AIH and PSC that include the anti-B cell-activating factor receptor monoclonal antibodies, nor-UDCA, amongst others, but the efficacy in patients with cirrhosis has not been fully established.

Summary Cirrhosis is present in 30–50% of patients at the time of diagnosis of AIH, in 20% of patients with PBC, and in 35% of patients with PSC. Therefore, cirrhosis constitutes one of the main complications of autoimmune liver disease and continues to develop at a frequency of approximately 3–6% per year. Patients with compensated AIH cirrhosis and histological inflammatory activity benefit of corticosteroid treatment. Patients with PBC and compensated cirrhosis should receive UDCA. OCA should be considered in non-responders but used with very close monitoring in patients with decompensated cirrhosis. There is no effective treatment option available for patients suffering from PSC. Liver transplantation is indicated for patients who have progressed to decompensated cirrhosis, and those with intractable symptoms or hepatocellular carcinoma within transplant criteria. Standard monitoring for cirrhosis-related complications is highly recommended.

Keywords Autoimmune liver disease · Autoimmune hepatitis · Primary biliary cholangitis · Primary sclerosing cholangitis · Cirrhosis

Introduction

Autoimmune Liver Diseases and Cirrhosis

Autoimmune liver diseases constitute a heterogeneous group of chronic liver disorders characterized by the development of parenchymal liver or biliary disease, associated with humoral and cellular immune response to "self" proteins. While autoimmune hepatitis (AIH) primarily affects the liver parenchyma [1•], primary biliary cholangitis (PBC) is a chronic disease that leads to the progressive destruction of the intrahepatic bile ducts [2]; primarily sclerosing cholangitis (PSC) is characterized by inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts [3•].

A significant proportion of patients with AIH under immunosuppressive treatment progress to liver cirrhosis. In patients with PBC, treatment with ursodeoxycholic acid (UDCA) can positively influence the progression of fibrosis, but in case of suboptimal treatment response, patients still have a considerable risk for the development of cirrhosis. There is no established treatment option for patients with PSC to control the disease and to prevent progression to cirrhosis. All

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autoimmune liver diseases, independent of their diagnosis, progress to cirrhosis.

For patients with compensated cirrhosis, disease-specific treatment should be continued in patients with AIH and PBC. For patients with PSC, no established specific treatment option is available. Management of complications is not disease-specific and follows general cirrhosis-related treatment guidelines. In all patients with autoimmune liver cirrhosis, screening for esophageal varices and for hepatocellular carcinoma (HCC) is recommended (Table 1), even though the risk for HCC is lower in patients with AIH, PBC, and PSC-associated cirrhosis than in patients with cirrhosis due to other etiologies.

Liver transplant (LT) is an option for all patients with decompensated cirrhosis secondary to autoimmune liver disease and can be instituted in specific situations, such as refractory pruritus in patients with PBC or recurrent episodes of cholangitis in patients with PSC. In addition, LT is indicated in patients with acute liver failure due to AIH who do not respond to steroids and in patients with HCC that are within the general criteria for LT. In these patients, LT will lead to a substantial improvement of life expectancy and of quality of life. Nevertheless, all autoimmune liver disease can eventually recur after LT.

It is recommended that patients with decompensated autoimmune liver cirrhosis should be followed in tertiary care centers with access to LT as a life-saving treatment option.

New treatment options for patients with autoimmune liver diseases are currently being investigated in clinical trials, but data specific for patients with liver cirrhosis is limited. Accordingly, it is not clear whether investigational agents are available or of clinical benefit to positively impact the evolution of autoimmune liver diseases in this patient population.

Autoimmune Hepatitis

Epidemiology

Autoimmune hepatitis is a female-predominant chronic liver disease characterized by immune-mediated destruction of liver parenchyma, interface hepatitis in liver biopsy, high serum immunoglobulin G (IgG), and presence of autoantibodies [1•]. While AIH is a rare disease, a recent study reported a near doubling in incidence between 1994 and 2012, reaching a point prevalence of 24/100,000 (35/100,000 for females) [4]. AIH occurs in all ethnic groups and in all age groups. A bimodal distribution has been described, with a higher incidence between the second and the third, and the fourth and the sixth decades of life. A significant proportion of patients develop AIH after 60 years of age [4].

Cirrhosis in Autoimmune Hepatitis

About 30% of adults and 50% of children with AIH have cirrhosis at the time of diagnosis [5]. Patients with cirrhosis related to AIH may present with nonspecific symptoms such as malaise, weight loss, and right upper quadrant discomfort or as acute exacerbation of chronic AIH [1•]. Patients presenting with acute disease with histological confirmation of cirrhosis likely suffered from preexisting, subclinical AIH for a considerable period. Patients may also present with decompensated cirrhosis or with complications of portal hypertension including ascites, hepatic encephalopathy, esophageal varices, and low platelet count.

The annual rate of progression to cirrhosis in patients without cirrhosis at diagnosis ranges considerably from 3 up to 40% of treated patients with AIH over time [6]. A recent study showed that AIH presenting as acute-on-chronic liver failure (ACLF) is not uncommon. In this setting, a low threshold for liver biopsy is important to corroborate the diagnosis, as nearly half of these patients with AIH can be seronegative [7•].

Patients with AIH cirrhosis have a reported risk of HCC ranging from 1 to 6% during follow-up [8, 9], with a 10-year probability of developing HCC of approximately 3%, which is significantly lower compared to most other etiologies of cirrhosis. The risk of developing HCC is higher in male patients, patients with immunosuppressive treatment for at least 3 years and with cirrhosis for at least 10 years [9].

Table 1 Screening and treatment of autoimmune liver disease in patient with cirrhosis

	Autoimmune hepatitis	Primary biliary cholangitis	Primary sclerosing cholangitis
Disease-specific treatment	Corticosteroids	UDCA	No specific treatment available
General cirrhosis-related treatment	Treatment of cirrhosis-associated complications (ascites, HE, HRS, esophageal varices, infections) according to general guidelines		
Screening	Esophageal varices HCC osteopenia/osteoporosis	Esophageal varices HCC osteopenia/osteoporosis	Esophageal varices CCA and HCC colorectal cancer

HCC hepatocellular carcinoma, *CCA* cholangiocarcinoma, *HE* hepatic encephalopathy, *HRS* hepatorenal syndrome

Risk Factors for the Development of Cirrhosis

African-American patients more commonly have cirrhosis at diagnosis of AIH [10]. Also, patients younger than 20 or older than 60 years, and males have a higher risk of cirrhosis at diagnosis (Table 2). Low serum albumin concentration, prolonged INR, and low platelet count are predictors of cirrhosis at the time of diagnosis for patients with AIH [11].

Progression to cirrhosis during treatment has been associated with HLA DR3/DR4 and worsening of the histological activity index in the liver biopsy [12]. The risk of progression to cirrhosis is higher in patients who have several relapses compared to those with sustained remission after their first treatment [13]. Lack of complete normalization of AST, ALT, and IgG within 1 year of treatment has also been associated with higher risk of cirrhosis [14]. Recently, we described that severe vitamin D deficiency (< 25 nmol/L) increases the risk of developing cirrhosis in patients with AIH. In addition, patients with persistent deficiency following vitamin D supplementation usually continue to have poor outcomes [15].

Treatment in Patients with AIH Cirrhosis

The main objective of corticosteroid therapy in AIH (Fig. 1) is to decrease liver injury, to prevent or revert fibrosis, and to enhance overall and LT-free survival. Treatment guidelines have evolved over time as compared to older recommendations, when improvement of AST and ALT below two times the upper limit of normal (ULN) were acceptable. Current guidelines recommend complete normalization of liver enzymes (AST, ALT) and IgG. Furthermore, a treatment duration for three or more years and normalization of liver biopsy findings before drug withdrawal are recommended [5]. Indeed, some patients' histological activity persists even if ALT and AST levels are normal [16].

Reduction in liver fibrosis and reversal of cirrhosis in AIH have been described in studies using protocol liver biopsies [17, 18••]. The first study demonstrating this finding was a retrospective analysis of paired liver biopsies from 28 patients who received treatment with prednisolone ± azathioprine. Improvement of hepatic fibrosis was observed in 57% and in 9 of 14 patients (64%) cirrhosis resolved after treatment. Regression of fibrosis was associated with the suppression of liver inflammation. These findings justified the recommendation that corticosteroid therapy be started early after diagnosis [19]. In another study of 87 treated AIH patients, histological cirrhosis disappeared in 8 of 14 patients with cirrhosis at presentation [18••]. Based on these findings, treatment of AIH patients with advanced fibrosis or cirrhosis is important and should be considered in all patients, if not contraindicated due to comorbidities.

Cirrhosis at diagnosis has been described as a factor associated with lower overall and LT-free survival [20]. However, a population-based study from New Zealand demonstrated that histological cirrhosis at diagnosis was not associated with poor prognosis and did not influence the response to initial corticosteroid treatment [11]. Similarly, a Chinese study reported the efficacy of initial corticosteroid treatment in patients with cirrhosis is comparable to that in those without cirrhosis. Importantly, patients with cirrhosis that were not treated had poor long-term outcomes [21]. Improvement of

Table 2 Risk factors for progression to cirrhosis in autoimmune liver disease

Autoimmune hepatitis	Primary biliary cholangitis	Primary sclerosing cholangitis
At diagnosis RF for cirrhosis - African-American patients [10] - Male patients - Patients < 20 or > 60 years - Low serum albumin [11] - Elevated INR [11] - Low platelet count [11] During treatment RF for progression to cirrhosis - Absence of complete response to treatment within 1 year [14] - HLA DR3/DR4 [12] - Worsening histological activity index in liver biopsy [12] - Patients who relapse [13] - Severe vitamin D deficiency (< 25 nmol/L) [15] - Non-response to vitamin D supplementation in deficient patients [15]	At diagnosis - Elevated alkaline phosphatase and bilirubin [30] - Young age [43] During treatment RF for progression to cirrhosis - Inadequate response to UDCA treatment	At diagnosis RF for poor outcome - Higher age at diagnosis - Male sex [71] - Classical form (in comparison with small duct disease) [71] - UC (in comparison with Crohn's disease) [71, 79] - Higher stage [79] - Elevated bilirubin [79] - Splenomegaly [79]

RF risk factors, *UC* ulcerative colitis

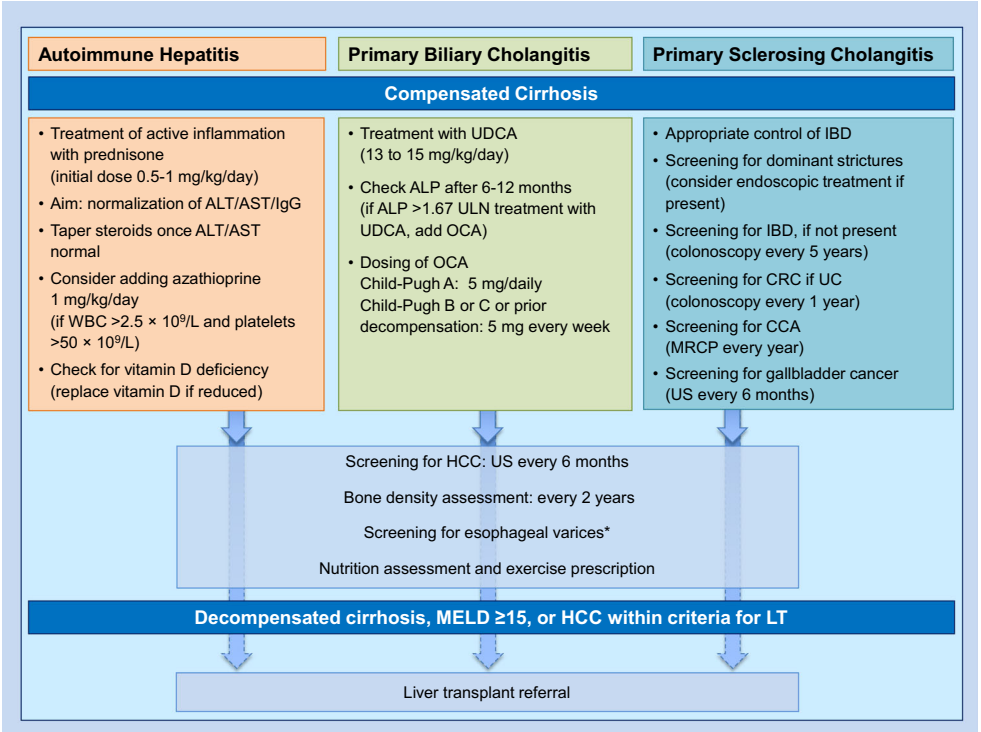

Fig. 1 Management strategies for patients with cirrhosis related to autoimmune liver disease. ALP = alkaline phosphatase, OCA = obeticholic acid, CCA = cholangiocarcinoma, CRC = colorectal cancer, HCC= hepatocellular carcinoma, UDCA = ursodeoxycholic acid, IBD = inflammatory bowel disease, MRCP (magnetic resonance cholangiopancreatography), US = ultrasound, * = screening interval depends on clinical findings

fibrosis after corticosteroid treatment might explain previous findings of similar survival rates between patients with and without cirrhosis at diagnosis [11].

For induction of remission, prednisone or prednisolone should be started between 0.5 and 1 mg/kg/day and consecutively tapered down. Azathioprine (AZA) in a low dose of 1 mg/kg/day [22] can be used as steroid sparing agent. Mycophenolate mofetil (MMF) is a treatment option for patients intolerant of AZA [23]. Importantly, AZA or MMF should be avoided in patients with severe cytopenia, with white blood cell counts below 2.5×10^9/L or platelet counts below 50×10^9/L.

Budesonide, a corticosteroid with a high first pass elimination by the liver, should not be used in patients with AIH cirrhosis, as a decrease of the metabolic function of the liver leads to increased plasma levels and its use in cirrhosis is associated with risk of portal vein thrombosis [24].

Overall, patients with decompensated AIH cirrhosis have more drug-induced side effects because of hypoalbuminemia, hyperbilirubinemia, and portosystemic shunting that can affect protein-binding and disposition of free prednisolone [25].

Patients with difficult to control diabetes, osteoporosis and vertebral compression fractures, or psychosis must be evaluated case by case for treatment benefit before the administration of corticosteroids [5, 26]. In general, treatment is not indicated in patients with AIH cirrhosis without histologic signs of inflammation on biopsy (burned out cirrhosis), as there is no benefit in overall outcomes [27].

We recommend measuring vitamin D levels in all patients with AIH and supplementation of vitamin D in case of deficiency [15].

Primary Biliary Cholangitis

Epidemiology

Primary biliary cholangitis predominantly affects female patients and patients who are typically older than 40 years. PBC does not present in childhood and the prevalence of PBC in women over the age of 40 years is estimated at 1 in 1000 [28].

Cirrhosis in Primary Biliary Cholangitis

Primary biliary cholangitis is characterized histologically by immune-mediated destruction of the interlobular bile ducts. Currently, most patients with diagnosis of PBC are asymptomatic at presentation and do not need a liver biopsy to establish diagnosis. Up to 23% may have evidence of cirrhosis at diagnosis [29]. Older studies suggest that most patients suffering from PBC have a chronic progressive course of the disease with an increase of the stage of fibrosis over time. For example, progression from early stage disease to extensive fibrosis has been reported in 34% of patients without treatment, whereas patients treated with UDCA had a significantly reduced risk for progression of approximately 7% [30]. Patients

with stage I histology demonstrating inflammation limited to the portal space and stage II with inflammation involving periportal areas as well showed progression to cirrhosis in 31% and 50%, respectively, in the absence of treatment [31]. In contrast, regression of fibrosis stage is seen only in a minority of patients (3% per year), independent of treatment with UDCA or without treatment [30].

Risk Factors for the Development of Cirrhosis

Risk assessment for patients with PBC was introduced in 1983 with the Yale model that identified elevated serum bilirubin, age, hepatomegaly, and advanced fibrosis or cirrhosis as independent predictors of poor prognosis [32]. With the introduction of the Mayo score, risk could be predicted without the need of a liver biopsy. Risk factors included age, serum bilirubin and albumin, prothrombin time, and severity of edema. More recently, a meta-analysis of data from almost 5000 PBC patients demonstrated that levels of alkaline phosphatase (ALP) and bilirubin can predict outcomes and could be used as surrogate end-points in therapy trials [33].

The main risk factor for development of cirrhosis (Table 2) is inadequate response to treatment to UDCA, and several binary scores have been developed to predict prognosis [30, 34–39]. Recently, dimensional scoring systems such as the GLOBE [40•] and the UK-PBC scores [42] have been developed and validated, and these should preferentially be used in clinical practice. Notably, a younger age at presentation, less than 50, not only predicts a more rapid disease process as compared to older patients but also increased risk of recurrent disease following liver transplantation [43].

Treatment in Patients with Cirrhosis

UDCA

Independent of the stage of disease, the first-line treatment of PBC is UDCA in patients with biochemical cholestasis (Fig. 1). However, response to treatment is more favorable in earlier stages. The optimal treatment dose is 13 to 15 mg/kg/day, usually given in two doses. Treatment with UDCA is associated with improved liver biochemistries and LT-free survival. Furthermore, UDCA reduces serum low-density lipoprotein cholesterol levels, the risk for esophageal varices, and histologic progression, whereas pruritus and fatigue are not affected [44].

Obeticholic Acid

Obeticholic acid (OCA) is currently licensed as second-line treatment for patients with inadequate response or intolerance to UDCA, defined as ALP ≥ 1.67 ULN after 1 year of UDCA treatment. In a long-term clinical impact and cost-effectiveness analysis, combined treatment with UDCA and OCA was determined to decrease the 15-year cumulative incidences of decompensated cirrhosis (12.2 to 4.5%), HCC (9.1 to 4.0%), and liver-related death (16.2 to 5.7%) and to increase the 15-year LT-free survival from 61.1 to 72.9% [45].

In patients with Child–Pugh A cirrhosis, OCA should be prescribed in a dose of 5 mg/day, whereas in patients with Child–Pugh B or C or prior decompensation the recommended dose is 5 mg/week for the first 3 months of treatment. OCA may then be increased to 5 mg two times per week, to a maximum of 10 mg twice a week. So far, OCA has not been investigated in detail in patients with decompensated cirrhosis. Taking into account a warning issued by the Food and Drug Administration in September 2017, the use of OCA in patients with decompensated cirrhosis outside the context of clinical trials is currently not recommended [44].

Fibrates

Fibrates are activators of the peroxisome proliferator activator receptor (PPAR), a nuclear receptor with the three subtypes α, δ, and ϒ. PPAR α is involved in the regulation of bile acid synthesis and detoxification, but PPAR-ϒ may also have a beneficial effect regarding cholestasis in patients with PBC. Currently, fibrates are only approved as lipid-lowering agents. Bezafibrate, a pan-PPAR agonist, was recently reported to be effective in lowering hepatic biochemistry in a multicenter clinical trial in patients with inadequate response to UDCA. In addition to 67% of patients normalizing ALT, subjects treated with bezafibrate also had an improvement in pruritus and elastography measurements. Of patients included, 54% had an advanced stage of disease with bridging fibrosis (Ludwig stage 3) or cirrhosis (Ludwig stage 4). In patients with cirrhosis, no significant increase in total bilirubin was observed compared to the placebo group. Since a high ALP and portal hypertension were identified as baseline risk factors for treatment failure, patients with severe cholestasis and advanced cirrhosis may not be ideal candidates for this treatment [46••].

New Options

Drugs under evaluation for PBC therapy include selective PPAR-δ agonists (seladelpar) [47] and non-steroidal FXR agonists, but currently there is not sufficient evidence to recommend their use in patients with PBC-related cirrhosis.

Pruritus

Pruritus is a frequent symptom in patients with PBC that negatively affects quality of life. Several pathophysiological mechanisms have been characterized including a role of bile acids, endogenous opioids [48], and lysophosphatidic acid [49], explaining the mode of action of treatment with bile acid

sequestrants, opioid antagonists, and rifampicin. Cholestyramine is a non-absorbable resin that is normally used as first-line therapy, at a dose of 4–8 g twice a day, given 2–4 h before or after other medications (UDCA or OCA) as they interfere with intestinal absorption. Rifampicin at a dose of 150–300 mg/day is a second-line treatment. However, monitoring liver biochemistries is recommended during its use as there is a risk of hepatotoxicity. Opiate antagonists (naltrexone) and selective serotonin reuptake inhibitors (sertraline) could be used as a third-line therapy [28].

Prophylactic Measures

Bone mineral density should be measured every 2 years, since the risk for osteopenia and osteoporosis is increased in patients with PBC and the severity of liver disease correlates with the severity of bone disease [50]. In patients with cholestasis, monitoring of fat-soluble vitamins is recommended [44].

Prognosis

In the UDCA era, LT-free survival determined using the GLOBE score is calculated at 90%, 77.5%, and 65.6% at 5, 10, and 15 years, respectively [42]. In the UK-PBC risk score analysis, overall event free survival after 5, 10, and 15 years was determined to be 96%, 89%, and 86% with events defined as liver-related death, LT or first bilirubin ≥ 100 μmol/L [40•]. In this analysis with a median follow-up of 6.3 years and a total of 23,673 patient-years, 260 patients had a LT (8.2%) and 31 patients (1%) died due to liver-related disease. Whereas the overall progression of fibrosis is relatively slow in patients with F3 or below, in patients with cirrhosis, the liver stiffness increases significantly over 5 years. An increase of 2.1 kPa/year in transient elastography has been associated with an 8.4-fold increased risk in liver decompensation, LT, and death [51].

Risk for and Treatment of Cancer

Patients with PBC have a slightly increased risk for HCC compared to the general population. Risk factors are male gender and advanced disease as well as suboptimal response to UDCA. Screening for HCC with ultrasound or a cross-sectional imaging technique is recommended every 6 months [44]. Treatment of HCC is similar as in cirrhosis due to other etiologies.

Primary Sclerosing Cholangitis

Epidemiology

Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized by multifocal bile duct strictures and progressive liver fibrosis. Most patients have coexistence of inflammatory bowel disease (IBD). PSC has a prevalence of up to 16.2 per 100,000 population and is classified as a rare disease. The prevalence is highest in northern Europe and low in Asia [3•] and two thirds of patients affected are male. Time from diagnosis until LT or PSC-related death was 13.2 years in a transplant centers analysis and 21.3 years in a community base survival analysis [52].

Risk Factors for the Development of Cirrhosis

Several prognostic models have been established for patients with PSC. The Mayo score integrates age, bilirubin, AST, and albumin as well as history of variceal bleeding in a prognostic model to assign patients into low-, intermediate-, and high-risk groups [53]. A recent study from a large international cohort of patients with PSC demonstrated that older age at diagnosis was associated with significantly lower LT-free survival, whereas female sex, Crohn's disease (relative to ulcerative colitis), and small duct PSC (relative to classical PSC) were identified as being protective [54••].

Pharmacologic Treatment in Patients with Cirrhosis

To date, there is no established medical treatment for patients with PSC. UDCA in a dose of 13 to 15 mg/kg/day has been shown to improve serum liver parameters, but had no effect on symptoms or clinical significant outcomes, such as histologic progression, LT, or liver-related death [55]. Treatment with a higher dose (28 to 30 mg/kg/day) was also associated with biochemical improvement but the study was stopped prematurely because of an enhanced risk of LT or serious adverse events, especially in patients with advanced disease [56].

The use of corticosteroids or alternative immunosuppressive agents is not associated with an improvement in outcome or disease activity [57]. However, in patients with elevated serum IgG4 (> 140 mg/dL) immunosuppression with prednisone/prednisolone may be a treatment option if IgG4-associated cholangiopathy cannot be excluded.

Treatment of IBD is performed according to standard treatment guidelines. In patients with decompensated cirrhosis, pharmacokinetic alteration, and especially a decreased first pass effect have to be taken into account, as this can lead to a significant increase of systemic exposition to drugs (i.e., budesonide) [25].

Non-pharmacologic Treatment in Patients with Cirrhosis

Dominant strictures of the biliary tract defined as a stenosis with a diameter of ≤ 1.5 mm in the common bile duct and/or ≤ 1.0 mm in a hepatic duct within 2 cm of the main

hepatic confluence should be evaluated for malignancy with ductal sampling with endoscopic retrograde cholangiopancreatography (ERCP) (brush cytology, biliary biopsies). Dominant strictures should be treated with endoscopic balloon dilatation, preferentially without performing plastic stent insertion [58•, 59•]. Percutaneous transhepatic biliary accesses are alternative treatment options in patients with failed crossing of strictures during ERCP [60].

Prophylactic Measures

Bone mineral density examination is recommended at diagnosis and thereafter in 2–3 years intervals, since osteoporosis is found in 4 to 10% of patients with PSC. Treatment with calcium, vitamin D, and bisphosphonates is recommended according to general guidelines. In patients with esophageal varices, a parenteral bisphosphonate should be used [57]. In patients with PSC and recurrent bacterial cholangitis, prophylactic rotating antibiotics may be indicated [60].

Prognosis

Asymptomatic patients with PSC have a better prognosis than patients with symptoms, but may become symptomatic over time [60, 61]. The Mayo PSC risk score utilizes the patient age, bilirubin, albumin, AST, and a prior history of variceal bleeding and was developed to predict short-term mortality [62]. More recently, the PSC risk estimate tool (PREsTo) has been used to predict decompensation and is reportedly more accurate than MELD score, Mayo PSC risk score, and ALP < 1.5× ULN [63•].

PSC and Cancer

Patients with PSC have an increased risk for the development of a cholangiocarcinoma (CCA), with a cumulative 10-year incidence between 7 and 9%. Several risk factors for the development of a CCA have been identified, such as elevated bilirubin, proctocolectomy, variceal bleeding, chronic ulcerative colitis with colorectal cancer or dysplasia, the duration of IBD, and polymorphisms of the natural killer cell receptor G2D (*NKG2D*) gene [57, 64]. Patients with PSC also have a 5-fold higher risk for the development of colorectal cancer compared to patients with IBD without PSC, warranting regular surveillance colonoscopy from the time of diagnosis [60, 65]. In contrast, the risk for HCC seems to be lower than in patients with cirrhosis of other etiologies [66].

General Considerations Regarding Management of Patients with Cirrhosis Due To Autoimmune Liver Disease

HCC Screening

Screening for HCC is recommended in all patients with cirrhosis independent of the etiology of the liver disease (Table 1), with ultrasound (US) every 6 months or a cross-sectional image technique suitable for the detection and characterization of focal liver lesions [67, 68].

Screening for Esophageal Varices

Patients with cirrhosis should be screened with upper endoscopy for esophageal varices every 2 to 3 years [69]. In patients with PSC, screening for esophageal varices should also be performed in non-cirrhotic patients with signs for portal hypertension [3•, 70].

Liver Transplantation in Autoimmune Liver Disease

Liver transplantation is a treatment option for all patients with autoimmune liver disease progressing to decompensated cirrhosis with a MELD score of ≥ 15 and for patients presenting with HCC within transplant criteria. In addition, patients with intractable pruritus (PBC) or chronic recurrent cholangitis (PSC) should be consider for LT, given that local and general criteria for LT are fulfilled [44, 71].

Follow-Up After LT

Autoimmune liver diseases may eventually recur after LT. In patients with AIH, optimal disease control prior to LT as well as maintenance treatment with low-dose steroids is associated with a reduced risk of recurrence [72, 73]. The risk for recurring PBC might be reduced with continuing treatment with UDCA post-LT, but this data needs to be confirmed in prospective studies [74]. For patients with PSC, so far no treatment option has been identified that influences the risk for recurrence. Re-transplant is a treatment option for all autoimmune liver diseases.

Future Directions

New Treatment Options

For patients with PBC, FXR agonists are a new treatment class and OCA is the first molecule of this group that has been

approved for non-responders to UDCA. Others FXR agonists are still in clinical testing. Although the label of OCA includes patients with cirrhosis, these new treatments need further in-depth evaluation in patients with decompensated cirrhosis [75••].

Currently, norursodeoxycholic acid is investigated in patients with PSC and available results show a significant reduction of ALP with this compound [76•]. These results need further confirmation and data in cirrhosis is currently lacking.

Rituximab is a monoclonal antibody against the CD20 antigen on the B cell surface. Treatment with two doses of 1000 mg IV 2 weeks apart was well tolerated in 22 patients with treatment-resistant type 1 AIH and none of those patients required termination of therapy or stated any side effects [77], but evidence in cirrhosis is needed. Anti-B cell-activating factor receptor (anti-Baff-R) monoclonal antibodies have been tested in Sjögren's disease [78] and a clinical trial in patients with AIH is currently ongoing (A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of ianalumab [VAY736] in Autoimmune Hepatitis (AMBER), ClinicalTrials.gov Identifier: NCT03217422). Whether this treatment could become a future treatment option for AIH cirrhosis is not yet known.

Conclusions

Autoimmune liver cirrhosis is a descriptive term addressing chronic advanced liver disease due to one out of several distinct autoimmune liver diseases. Autoimmune liver diseases may progress to compensated and finally decompensated cirrhosis, as a common pathway; however, each of the autoimmune liver diseases is associated with a distinct epidemiology, clinical phenotype, response to treatment, and evolution over time. In patients with AIH, development of cirrhosis can be prevented with optimal corticosteroid treatment. In the case of established cirrhosis, inflammatory activity should be treated, but a balance between optimal immunosuppression and the risk for complications has to be considered. Patients with PBC cirrhosis should continue treatment with UDCA, although UDCA is more effective in earlier stages of the disease. For PSC, no disease-specific treatment is available to date. Cirrhosis-associated complications are treated according to general guidelines for compensated and decompensated cirrhosis. Screening for esophageal varices and for HCC is recommended independent of the etiology of liver disease. Additional screening measures should be considered based on the etiology of cirrhosis, i.e., screening for CCA.

Liver transplant should be considered for all patients with decompensated cirrhosis due to autoimmune liver disease and may be considered for disease-specific complications, such as refractory pruritus in PBC and recurrent cholangitis in PSC. However, all autoimmune liver diseases may recur after LT.

Compliance with Ethical Standards

Conflict of Interest Aldo Montano-Loza, Andrew Mason and Maryam Ebadi each declare no potential conflicts of interest. Guido Stirnimann reports personal fees from Intercept Switzerland, during the conduct of the study.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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