INTRODUCTION

The term autoimmune liver diseases (AILD) includes three different entities: primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH). The aetiologies are unknown and the pathogenesis of these diseases is poorly understood. A better understanding of the aetiology of these entities should improve the diagnosis and treatment of AILD patients and prevent liver-related mortality and transplantation.

Abstract

Autoimmune liver diseases (AILD), namely autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), are rare diseases. These days, patients with PBC almost never require liver transplantation. When treated early with ursodeoxycholic acid patients have a normal life expectancy if the disease is diagnosed at an early stage and the patients respond to treatment. Patients with AIH often go into remission with first-line therapy including corticosteroids alone or in combination with azathioprine. Nevertheless, about one quarter of patients already developed cirrhosis at diagnosis. Those who do not respond to first line standard of care (SOC) have significant liver-related morbidity and mortality. No approved second- or third-line treatments are available and the drugs are selected based on limited case series and personal experience. Larger trials are needed to develop efficient therapies for difficult-to-treat AIH patients. No treatment has been found to alter the natural course of disease in patients with PSC except for liver transplantation. Identifying PSC patients at risk of developing cholangiocarcinoma (CCA) is another unmet need. Current research in all AILD including AIH, PBC and PSC, focuses on improving our understanding of the underlying disease process and identifying new therapeutic targets to decrease morbidity and mortality.

Keywords

autoimmune hepatitis, cholangiocarcinoma, primary biliary cholangitis, primary sclerosing cholangitis, regulatory T cells
Primary biliary cholangitis, a non-suppurative destructive cholangitis, is the archetype of an autoimmune disease. Women are affected more often (approximately 9:1) than men and well-defined antibodies targeting the E2 subunit of the pyruvate dehydrogenase complex are a diagnostic hallmark. PBC is associated with a variety of other autoimmune disorders, for example celiac disease, autoimmune thyroid disorders and systemic lupus erythematosus, to name a few. Originally PBC was called primary biliary cirrhosis because patients were often diagnosed in advanced stages of the disease. At present, due to improved techniques, PBC patients are diagnosed in earlier stages with less advanced fibrosis. In the 1980s, PBC was a leading indication for liver transplantation but, nowadays, liver transplantation for PBC is a rare event. Therefore, the name was changed to PBC to mirror the current prognosis of PBC. PBC patients, who are diagnosed at an early stage of the disease and who respond to ursodeoxycholic acid (UDCA) therapy have a life expectancy similar to age- and sex-matched controls. These patients no longer develop end-stage liver disease and the need for liver transplantation is rare. Disease progression is stopped if alkaline phosphatase (ALP), a surrogate marker for inflammation of the bile ducts, normalises or drops by more than 40% within one year after the initiation of UDCA therapy (13-15 mg/kg body weight daily) (Barcelona criteria).

There are multiple definitions for UDCA treatment failure. UDCA treatment failure occurs in 25%-50% of these patients depending on the criteria. Non-response one year after treatment initiation places these patients at a higher risk of disease progression, including the development of hepatocellular carcinoma and end-stage liver disease.

The POISE (Phase 3) trial evaluated obeticholic acid (OCA), a farnesoid-X-receptor (FXR) agonist for the treatment of patients with PBC who did not achieve a reduction in ALP with UDCA to less than 1.67 × upper limit of normal (ULN) or in bilirubin to below 2 × ULN. The primary endpoint was ALP <1.67 × ULN with at least 15% ALP-reduction and normalization of bilirubin at 12 months. This endpoint was reached both in the 5-10 mg OCA group (with or without UDCA) and the 10 mg OCA (with or without UDCA) group in 46% and 47% respectively. Patients in the placebo group (with or without UDCA) reached the primary endpoint in 10% of cases. As expected, the major side effect of OCA treatment was dose-dependent pruritus, which led to discontinuation of treatment in up to 10% of patients. In addition, an increase in LDL-cholesterol was observed and the long-term cardiovascular risk in PBC patients treated with OCA must still be determined. In 2018, the BEZUROSO (phase 3) trial was published, evaluating bezafibrate in combination with UDCA in non-responders. The primary endpoint was complete biochemical remission after 24 months. Roughly one third of all patients reached this primary endpoint and two thirds achieved normalized ALP values with bezafibrate. The main side effects in the bezafibrate group were a 5% increase in creatinine values due to a pharmacological effect, not caused by reduced kidney function, and myalgia in 20% of patients (10% of patients had myalgia in the placebo group). Although bezafibrate has not yet been approved for the treatment of PBC, it is an appealing off-label treatment option in non-responders to UDCA treatment, with a favourable side-effect profile and low treatment costs. A recent small trial from Leuven, Belgium, evaluated the additive effects of bezafibrate in patients who did not respond adequately to dual therapy with OCA and UDCA. Triple therapy (bezafibrate, OCA, UDCA) lowered cholestatic parameters and improved pruritus in most patients. There are ongoing trials to clarify the mechanism of action of bezafibrate, which is an agonist for the peroxisome proliferator-activated receptor (PPAR). While this agent works as an agonist on different PPARs, selective PPAR-δ- (Seladelpar; CYMABAY) or PPAR-α/δ-agonists (Elafibranor; GENFIT) are also under evaluation in phase III trials for PBC to improve the efficacy and reduce side effects in patients who do not respond to UDCA therapy. Seladelpar demonstrated anti-cholestatic properties and improved pruritus in both patients with and without cirrhosis (Child A) and elafibranor has also been shown to have anti-cholestatic effects associated with a reduction in pruritus. Another trial in PBC is evaluating the use of the fibroblast growth factor 19 (FGF19) agonist NGM282 (NGMBio). FGF19 is mainly located in the ileum and serves to regulate bile acid metabolism. Production of FGF19 is induced by bile acid-dependent activation of the FXR receptor. FGF19 translocates via the portal system to the liver and suppresses expression of the rate-limiting enzyme for de novo bile acid synthesis in the liver (CYP7A1). In a small 28-day trial, NGM282 improved ALP by at least 15% from baseline.

In summary, PBC, as a role model for autoimmune diseases in general and liver diseases in particular, is no longer a major indication for liver transplantation. PBC patients who are diagnosed early and respond to UDCA have a normal life expectancy. New PBC treatments, in particular OCA, have recently been approved in non-responders to UDCA. New agents are under investigation in PBC patients to further improve efficacy and tolerance.
3 | PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis is a rare liver disease that significantly affects quality of life, morbidity and mortality. The aetiology of PSC is unknown and its pathogenesis is poorly understood. The only existing life-saving treatment option is liver transplantation. Nevertheless, PSC reoccurs in 20%-37% of patients after liver transplantation.11 No drugs have been shown to be effective in preventing death, liver transplantation or cholangiocarcinoma (CCA). Although UDCA improves ALP, it does not improve survival. The role of ALP as a surrogate marker for treatment response is a subject of debate. The prognosis is poor in patients with PSC; up to 40% require liver transplantation and up to 31% develop CCA. Inflammatory bowel disease (IBD) is present in most cases.12,13 The diagnosis of PSC is mainly based on imaging, in particular endoscopic retrograde cholangio-pancreatography and magnetic resonance cholangio-pancreatography. Strictures and prestenotic dilatations of the large and medium-sized intra- and extrahepatic bile ducts are characteristic features. Sclerosing cholangitis from other causes must be excluded, for example, ischemic-type biliary lesions after liver transplantation, secondary sclerosing cholangitis usually after long-term intensive care, or IgG4-related cholangitis. Liver histopathology typically shows concentric ‘onion-skin-like’ fibrosis around the bile ducts, which is often accompanied by elevated cholestatic laboratory test results. It has been hypothesized that the pathogenesis of PSC is multifactorial, but it is poorly understood. Various therapeutic agents are under investigation for PSC with multiple molecular targets (e.g. FXR, PPAR, adhesion molecules and the microbiota) in different organs (e.g. liver and gut). Improving the understanding of the aetiopathogenesis of this disease can help identify future therapies. Recent published studies support a potential role for bacterial translocation from the gut to the liver due to intestinal barrier dysfunction. Nakamoto et al14 showed that klebsiella pneumoniae, proteus mirabilis and enterococcus gallinarum were prevalent in patients with PSC and responsible for bacterial translocation as well as for hepatobiliary inflammation in gnotobiotic mouse models. The progression of hepatobiliary disease was promoted via a TH17 response.14 Therefore antibiotic therapy might be beneficial in the natural course of PSC.

It is also urgent to improve the risk stratification of unfavourable outcomes in patients with PSC. Recent studies have shown that elevated Immunoglobulin G (IgG) at diagnosis is an independent predictor of transplant-free survival.15 The Amsterdam-Oxford model has been proposed to stratify the risk of liver transplantation or death in PSC patients using seven available variables (albumin, platelet count, age, PSC subtype, aspartate-aminotransferase, ALP and bilirubin).16 New biomarkers are needed to diagnose PSC, predict disease outcome and serve as monitoring parameters. Bile proteomic profiles might help identify PSC patients at risk of developing CCA, thus facilitating early diagnosis of CCA and improving the prognosis by reinforcing screening for malignancy.17 Because UDCA has not been found to improve the outcome of liver disease in patients with PSC, new therapies are urgently needed. Recent evidence has supported a link between the liver and the gut in the pathogenesis of PSC. The potential impact of IBD therapies on PSC were evaluated based on the strong association between PSC and IBD. A retrospective analysis by Tse et al found initial improvement in ALP in patients with PSC and concomitant IBD who were treated with the anti-tumour-necrosis factor alpha (TNF) antibody, adalimumab.18 However, these findings were not confirmed when PSC patients were treated with another anti-TNF antibody, infliximab. No improvement in liver biochemistry was seen in patients with IBD and concomitant PSC receiving vedolizumab, an α4β7 integrin inhibitor.18 A recent trial investigated the feasibility and safety of faecal microbiota transplantation (FMT) in patients with PSC. Ten patients with PSC and concomitant IBD and an ALP >1.5 × ULN were included and received a single FMT via colonoscopy. A more than 50% decline in ALP levels was observed in 30% of patients and no adverse events occurred.19 Thus, further evaluation of FMT is needed in patients with PSC and IBD. The non-steroidal FXR-agonist, clofexor has been shown to improve cholestasis and liver injury in a small trial with 52 patients who were randomized to receive a placebo and two groups with different doses of clofexor. Treatment with the maximum dose of clofexor over a period of 12 weeks led to a 21% decrease in ALP and to significant improvement in aminotransferase levels.20 Nor-UDCA, a side-chain modified derivate of UDCA, had dose-dependent beneficial effects on ALP values in a phase II trial.21 A phase III study with NoUDCA for PSC is ongoing. Rupp et al showed that endoscopic bile duct dilatation was beneficial in patients with PSC in a large retrospective study.22 PSC patients with a dominant bile duct stricture received either endoscopy with or without bile duct dilation at defined intervals or in case of clinical symptoms, an approach that does not follow current recommendations from European and American guidelines. The outcome in patients who received scheduled dilation therapy was significantly better for transplant-free survival and time to transplantation, with a reasonable safety profile and no increase in intervention-associated adverse events. This study is worth noting because it chose hard endpoints such as transplant-free survival while previous studies have only used ALP as a surrogate marker. Nevertheless, hard endpoints such as death or the need for liver transplantation are difficult to assess in clinical trials of such a rare disease. New biomarkers are needed that are more robust than biochemical markers such as ALP. Finally any new drug for PSC should be evaluated for hard endpoints such as death or transplant-free survival. Furthermore, risk stratification of PSC subgroups must be improved to effectively analyse potential improvements in mortality or the need for liver transplantation with any new agents. Because patients with PSC with or without associated IBD are a heterogeneous group with a variety of disease phenotypes, a more individualized approach may be needed for multimodal treatment options in the future.

4 | AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is characterized by elevated aminotransferases, hypergammaglobulinaemia, the presence of characteristic
auto-antibodies (e.g., anti-nuclear antibodies [ANA] and smooth muscle antibodies [SMA]) in AIH type 1, liver-kidney-microsome antibodies [LKM] in AIH type 2) and histopathological features such as plasma cell enriched infiltrates, emperipolise and interface hepatitis. Neither histopathology, auto-antibodies or hypergammaglobulinaemia alone can diagnose AIH. All of these features and the exclusion of other liver diseases are necessary to make the diagnosis of this disease, which can be confirmed by a response to corticosteroids. New diagnostic markers are needed to diagnose AIH as well as to monitor treatment response. Existing auto-antibodies either lack sensitivity or specificity or both. Although the sensitivity and specificity of ANA and SMA are acceptable, they are not specific for AIH. Anti-soluble-liver-antigen antibodies and LKM-antibodies are highly specific but their sensitivity is limited. Although anti-asialoglycoprotein receptor antibodies have the best overall performance, they are not widely available. We recently showed that anti-huntingtin-interacting protein 1-related protein (anti-HIP1R protein) antibodies, measured using enzyme-linked immunosorbent assay, were elevated in AIH patients with a higher specificity than and equal sensitivity to ANA and SMA. Normalization of IgG and aminotransferases as well as a lack of inflammatory activity in liver histology are the main treatment goals, called complete remission. A subgroup of patients fails to achieve remission with corticosteroids and/or azathioprine, which are the only approved agents for the treatment of AIH. Large randomized, controlled trials that evaluate the efficacy and safety of other immunosuppressive drugs except for budesonide, are lacking. Second- and third-line therapies are used off-label in daily clinical practice for treatment failures or intolerance to standard of care (SOC) with corticosteroids alone or combined with azathioprine. Mycophenolate mofetil is the second treatment of choice in patients who do not tolerate azathioprine. Several drugs are used in non-responders to first line treatment with SOC, including calcineurin inhibitors such as cyclosporine A and tacrolimus. However, none of these drugs have been approved for this indication. Although Weiler-Norman et al. showed that anti-TNF-antibodies induced remission in a series of difficult-to-treat patients, infectious complications developed in up to 70% of these patients. However, several case reports indicate that TNF-antibodies may even cause AIH. Rituximab, a B-cell depleting agent, has been shown to induce remission in hard-to-treat AIH patients with lower complication rates. Another B-cell depleting monoclonal antibody targeting the B-cell activation factor receptor is under investigation in a phase II/III trial in AIH patients who do not respond to SOC. Furthermore, there is a reduced balance of regulatory and effector T cells in patients with AIH who do not achieve remission. Interleukin-2 (IL-2) is a key cytokine for T-cell tolerance and IL-2 therapy has shown to restore immune tolerance by restoring impaired regulatory T-cell function. A case report of low dose IL-2 therapy with 1 million units five times a month for six months showed an increase in regulatory T cells and induced remission in one of two treated AIH patients. Data on the transfer of regulatory T cells in humans for this indication will soon be available. Both IL-2 therapy and the transfer of regulatory T cells are promising strategies, which require further investigation in larger trials. Because AIH is a rare disease and most patients respond to first line therapy, large prospective multicentre studies are difficult. Nevertheless, a multicentre international trial is urgently needed to perform robust studies for salvage therapies in patients with AIH and an incomplete response or intolerance to SOC. The European Reference Network (ERN) for rare liver diseases could facilitate the implementation of these studies in the future.

5 | SUMMARY

Overall, PBC is probably the best understood and well managed autoimmune liver disease. Two approved treatments and one off-label treatment are used in clinical practice. PBC patients have a normal life expectancy if they are diagnosed early, and if they respond to treatment. The goal of current trials for PBC is to maximize the response rate in non-responders to UDCA while maintaining a good safety profile. Research in AIH is focused on a better understanding of the pathogenesis of the disease to improve diagnosis and treatment. Available diagnostic tests lack specificity and sensitivity. Thus, the diagnosis of AIH often remains a clinical challenge because specific tests are not available and the diagnosis is based on several parameters and the exclusion of other liver diseases. New biomarkers are under investigation to meet this need. Treatment is mainly focused on patients who fail to achieve complete remission with the SOC (corticosteroids and/or azathioprine). Several second- and third-line agents, several of them approved for other autoimmune diseases, are available. New agents either targeting B lymphocytes or enhancing regulatory T lymphocytes are under investigation for the treatment of AIH patients who do not respond to first line SOC. PSC remains the ‘black box’ of hepatology. The aetiology is not understood and there are no treatment options except for liver transplantation. PSC is a significant risk factor for the development of CCA. Because the suggested aetiology is multifactorial, future management of PSC may be based on multiple approaches combining risk-stratification, effective screening strategies and drugs targeting different molecules and pathways optimizing the outcome of these patients. AILD are rare diseases. Multicentre prospective cohorts of patients with AILD are necessary for robust future trials to evaluate biomarkers, risk-scores and treatment options. The European Reference Network on hepatological diseases (ERN RARE-LIVER) might be the appropriate group to help implement these trials.

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CONFLICT OF INTEREST

Bastian Engel declares no conflict of interest related to this work. Richard Taubert is inventor of the patent application for the use of anti-HIP1R for the diagnosis of AIH. Elmar Jaeckel is inventor of the patent application for the use of anti-HIP1R for the diagnosis of AIH. Michael P. Manns is or was principal investigator for Falk Pharma, Gilead, Intercept and Novartis. He received grants from Falk Pharma, Gilead and Intercept. Michael Manns is or was a consultant for Falk Pharma, Gilead, Intercept, Roche and Novartis and he lectured for Falk Pharma and Gilead.
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