Primary Biliary Cholangitis: Disease Pathogenesis and Implications for Established and Novel Therapeutics

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Primary Biliary Cholangitis is a progressive, autoimmune cholestatic liver disorder. Cholestasis with disease progression may lead to dyslipidemia, osteodystrophy and fat-soluble vitamin deficiency. Portal hypertension may develop prior to advanced stages of fibrosis. Untreated disease may lead to cirrhosis, hepatocellular cancer and need for orthotopic liver transplantation. Classically, diagnosis is made with elevation of alkaline phosphatase, demonstration of circulating antimitochondrial antibody, and if performed: asymmetric destruction/nonsuppurative cholangitis of intralobular bile ducts on biopsy. Disease pathogenesis is complex and results from innate and adaptive (cell-mediated and humoral) responses that lead to inflammation of biliary duct epithelium. Ongoing damage is amplified and sustained through bile acid toxicity. Use of weight based (13-15mg/kg) ursodeoxycholic acid is well established in retarding disease progression and improving survival; however, is ineffective in achieving complete biochemical remission in many. Recently, a Farnesoid X Receptor agonist, obeticholic acid, has been approved for use. A number of ongoing clinical studies are underway to evaluate utility of fibric acid derivatives, biologics, antifibrotics, and stem cells as monotherapy or in combination with ursodeoxycholic acid for primary biliary cholangitis. The aim of this review is to discuss disease pathogenesis and highlight rationale/implications for both established and novel therapeutics. (J CLIN EXP HEPATOL 2016;6:311-318)

Primary biliary cholangitis (PBC) is a progressive, autoimmune liver disease resulting in chronic granulomatous lymphocytic cholangitis of the small bile ducts.¹ The classic triad of cholestasis, circulating anti-mitochondrial antibodies (AMAbs), and asymmetric destruction of intralobular bile ducts within portal triads on histopathology is diagnostic.² PBC incidence ranges from 0.33 to 5.8 per 100,000/year with prevalence 1.91 to 40.2 per 100,000.³ PBC predominantly occurs in women (10:1 female/male) and usually presents after the fourth decade.⁴ Generally, at the time of diagnosis, patients are asymptomatic and the two most common symptoms

developing longitudinally are nonspecific: fatigue and pruritus. Complications with chronic cholestasis in PBC include dyslipidemia, osteodystrophy, and fat-soluble vitamin deficiency. Portal hypertensive-related complications including gastroesophageal varices might develop prior to advanced stages of fibrosis.⁵ Classically, ursodeoxycholic acid was well established as the only therapy in retarding disease progression and improving survival, especially when initiated in early stages.^{6,7} However, ursodeoxycholic acid (UDCA) is ineffective in achieving disease remission in up to 30–40% of patients, warranting development of novel therapeutics. The aim of this review will feature aspects of disease pathogenesis and highlight implications for established and novel therapeutics.

PBC PATHOGENESIS

Expression of the PBC disease phenotype is a result of a complex series of events that trigger an aberrant, sustained and damaging effect on intralobular bile ducts. It is postulated that environmental exposure(s) (e.g. chemical substances and infectious agents) in a genetically susceptible individual trigger pathogenesis.⁸⁻¹³ One cohort study found that family history of autoimmune disease (e.g. PBC) and personal history of autoimmune disease, smoking, or recurrent urinary tract infections were significant

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Abbreviations: PBC: primary biliary cholangitis; AMAbs: anti-mitochondrial antibodies; IL: interleukin; MHC: major histocompatibility complex; ALP: alkaline phosphatase; GGT: gamma-glutamyltranspeptidase; ALT: alanine aminotransferase; ULN: upper limit of normal; OCA: obeticholic acid; CDCA: chenodeoxycholic acid; BA: bile acids; FXR: farnesoid X receptor; FGF-19: fibroblast growth factor; ASBT: apical sodium BA transporter; PPAR α : peroxisome proliferator-activated α -receptor; UC-MSC: umbilical cord mesenchymal stem cells
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risks factors for the development of PBC.⁸ The true inciting event eliciting host immune response is likely due to more than one environmental trigger and remains largely uncharacterized. Irrespective of source, innate and adaptive immune responses are primed that in turn drive ongoing inflammation and bile duct epithelial damage.

A distinct cellular and humoral immune response to intralobular bile ducts is demonstrated in PBC.¹⁴ Cytopathic examination reveals heavy infiltration by both CD4+ and CD8+ T cells that are reactive to conserved mitochondrial and nuclear antigens, including the 2-oxo-acid dehydrogenase complexes and particularly, E2 component of the pyruvate dehydrogenase complex—the principal target of circulating AMAb.¹⁴ A predominant CD4+ Th1 cytokine pattern with high levels of interferon- γ , interleukin (IL)-12, and IL-23 expression in liver tissue and the peripheral circulation is demonstrated.¹⁵ Chemokines (CXCL10, CXCL9, CX3CL1, and CCL20) secreted by inflamed cholangiocytes lead to recruitment and activation of more T-cells, which propagate and perpetuate the inflammatory response.¹⁶

Persistence of innate and adaptive immune responses generates chronic inflammation in bile duct epithelium that in turn lead to duct destruction/loss (ductopenia) and cholestasis. Chronic cholestasis results in systemic as well as intrahepatic accumulation of hydrophobic cytotoxic bile acids (BA, including chenodeoxycholic acid (CDCA), deoxycholic acid, and lithocholic acid) that cause liver cell injury and subsequently hepatocyte apoptosis.¹⁷ BAs generate reactive oxygen species that lead to cell shrinkage, activation of NADPH oxidase leading to mitochondrial injury, cytochrome c release, and apoptosis via the Fas ligand associated pathway.¹⁷ Apart from downstream signaling, BA directly activate hepatocytes to secrete pro-inflammatory cytokines that induce inflammation and fibrosis in surrounding tissue.^{17,18} Hepatocyte expression of major histocompatibility complex (MHC) class I is also induced by BAs, which provides another mechanism by which immune cell-mediated injury can occur.¹⁹

DIAGNOSIS

The diagnosis of PBC may be implicated in the setting of cholestatic liver injury and supported with demonstration of circulating AMAb—though the presence of AMA is not absolute and may be absent in 10% of cases.²⁰ The American Association for the Study of Liver Disease recommends that diagnosis be based on two of the three following criteria: “(1) biochemical evidence of cholestasis with elevation in alkaline phosphatase (ALP); (2) presence of AMAb; and (3) histopathological evidence of nonsuppurative cholangitis and destruction of small or medium-sized interlobular bile ducts on biopsy.²¹” No official cutoff for an AMAb positive titer exists; however, the European Association for the Study of the Liver considers an AMAb

titer of >1:40 as significant.²² Of importance, liver biopsy is not required if there is elevated ALP and an elevated AMAb, however, may have utility in fibrosis staging.

THERAPEUTIC AGENTS: ESTABLISHED

Ursodeoxycholic Acid

There are at least four mechanisms of action by which UDCA is thought to have therapeutic effect in PBC: “(1) increasing the hydrophilicity index of the circulating BA pool; (2) stimulation of hepatocellular and ductular secretions; (3) cytoprotection against BA and cytokine-induced injury; and (4) immunomodulatory/anti-inflammatory effects (Table 1).¹⁷” UDCA inhibits intestinal absorption of endogenous BAs and stimulates hepatocellular BA secretion while increasing the hydrophilicity BA pool, which leads to interruption of enterohepatic circulation and a fall in endogenous toxic hydrophobic BAs in the circulation and hepatic tissue.¹⁷ BA stimulation is secondary to an upregulation of specific bile acid exchangers, specifically, anion exchanger (AE2), which is usually downregulated by inflammatory cytokines expressed in PBC.^{23,24} UDCA administration allows for repletion of reactive oxygen species scavenger capacity and stabilization of hepatocyte membranes, conferring cytoprotection and abrogation of BA-induced hepatocyte apoptosis.^{25–27} UDCA also has the ability to downregulate MHC class I expression in the hepatocyte *in vivo*²⁸ as well as inhibit interferon inducible MHC class II *in vitro*,²⁹ thereby attenuating potentially damaging adaptive immune responses leading to inflammation.¹⁷

UDCA Effects on Biochemistries

In a seminal study, results of UDCA (13–15 mg/kg daily) on hepatic biochemical markers were prospectively evaluated in 15 patients with PBC.³⁰ Liver enzymes downtrended in every patient and, at 2 years, the average ALP, gamma-glutamyltranspeptidase (GGT), alanine aminotransferase (ALT), and bilirubin levels diminished by 78%, 65%, 68%, and 36% respectively when compared to pretreatment. In three patients who agreed to interrupt UDCA for 3 months after two years of therapy, recrudescence of cholestasis was observed, which again improved after UDCA re-initiation. These findings cemented UDCA as cornerstone of therapy in PBC.

UDCA Effects on Histologic Progression

Markov modeling was used in a French study to evaluate PBC progression between histologic nonfibrotic stages to fibrotic/cirrhosis stages. This was a randomized, double blind, placebo-controlled trial of UDCA therapy in 103 PBC subjects.³¹ Treatment with UDCA correlated with a 5-fold lower progression rate from early stage to late stage histologic disease—UDCA treated group 7% per year vs.

Table 1 Medical Therapy for Primary Biliary Cholangitis.

Agent	Rationale	Seminal/current study results and evaluations	Side effects
UDCA	<ul style="list-style-type: none"> Increases polarized BA pool Upregulates BA exchangers in biliary epithelium Oxygen radical scavenger Immunomodulator 	<ul style="list-style-type: none"> Improves liver biochemistries Delays histological progression Improves transplant-free survival Prevents recurrence after LTx 	<ul style="list-style-type: none"> Change in bowel habits Occasional headaches, dizziness
OCA	<ul style="list-style-type: none"> Activates FXR Hepatocytes: increased expression of BA export pumps Enterocytes: Decreases enterohepatic BA absorption & circulation Increases expression of FGF-19 <ul style="list-style-type: none"> Hepatocytes: decreases BA synthesis Enterocytes: decrease BA enterohepatic circulation 	<ul style="list-style-type: none"> Improves liver biochemistries <i>POISE Trial (NCT01473524, Phase III)</i>—effects on liver biochemistries <i>COBALT Trial (NCT0230811)</i>—outcomes including LTx and death 	<ul style="list-style-type: none"> Pruritus
Fibrates	<ul style="list-style-type: none"> Decreases expression of inflammatory cytokines Activates PPARα <ul style="list-style-type: none"> Hepatocytes: decreases BA synthesis & BA export from bile canalicular epithelium 	<ul style="list-style-type: none"> Improves liver biochemistries No survival benefits currently identified <i>BEZURSO Trial (NCT01654731, Phase III)</i>: primary aim- effects on liver enzymes; secondary aim- transplant-free survival 	<ul style="list-style-type: none"> Muscle pain, myositis Pruritus Heartburn Elevated transaminases
Budesonide	<ul style="list-style-type: none"> Anti-inflammatory through nuclear glucocorticoid receptors 	<ul style="list-style-type: none"> Improves liver biochemistries Possibly improves liver histology and delays progression <i>NCT00746486</i>—effects on treatment response 	<ul style="list-style-type: none"> Decreased immunity Decreased bone density Adrenal suppression Cutaneous changes Hirsutism Hyperglycemia Weight gain
Biologics	<ul style="list-style-type: none"> Specific monoclonal antibodies to antigens in the humoral immune response 	<ul style="list-style-type: none"> Rituximab—minimal effect on liver biochemistries Ustekinumab—no effect on liver biochemistries 	<ul style="list-style-type: none"> Decreased immunity Neuropathy

Abbreviations: BA: bile acid; LTx: liver transplantation; FXR: farnesoid X receptor; FGF-19: fibroblast growth factor-19; PPAR α : proliferator-activated α -receptor.

placebo group 34% per year ($P < 0.02$). At 4 years, there was a 76% (95% CI: 59–88) chance of persisting in earlier stages in the UDCA group, compared to 29% (15–52%) in placebo. After 8 years, these probabilities were 61% (38–80%) and 13% (6–32%), respectively. The predicted median time for development of extensive fibrosis was 12 years with UDCA vs. 2 years with placebo.

UDCA Effects on Survival

A subsequent large French cohort study aimed to determine 10-year survival of UDCA-treated patients using endpoints which included transplant-free survival and overall survival.⁶ 225 PBC subjects undergoing UDCA (13–15 mg/kg/day) therapy were followed. PBC subjects managed with UDCA had transplant-free survival significantly higher than expected. Upon subgroup analysis, survival was similar to control in the non-cirrhotic cohort but worse in the cirrhotic cohort, highlighting importance of UDCA administration in early stages of disease.

In another analysis of 262 patients receiving 13–15 mg/kg UDCA daily for a mean of 8 years, survival benefit was

demonstrated.⁷ Transplant-free survival at 10 years was 84% and 66% at 20 years. Transplant-free survival was higher than spontaneous survival rates forecasted by established prognostic models.³² Those patients treated in late stages of disease (III–IV) had increased risk of death or need for liver transplantation (relative risk: 2.2, $P < 0.05$)—again highlighting the importance of early usage.⁷ In a recent meta-analysis of 4845-pooled PBC subjects, overall transplant-free survival at 5 years, 10 years, and 15 years was 90%, 78%, and 66% respectively in UDCA-treated patients, compared with 79%, 59%, and 32% at 5 years, 10 years, and 15 years respectively in treatment naïve patients.³³

DEFINING BIOCHEMICAL RESPONSE

Of most importance, prognosis in PBC is determined by the biochemical response to therapy. A number of criteria to define biochemical response to UDCA exist (Table 2). These include the Barcelona Criteria, Paris-I Criteria, Toronto Criteria, Mayo Criteria, and recently, Paris-II Criteria which all have biochemical cutoffs to determine response.

Table 2 Established Criteria for Biochemical Response to Urosdeoxycholic Acid.

Criteria Author	Biochemical endpoints	Evaluation time	Clinical endpoints
Barcelona ⁶³ Parès	ALP 40% decrease or normalization	1 year	Transplant-free survival
Mayo ⁶⁴ Mohma	ALP < 2 times ULN and/or Mayo risk score <4.5	2 year	Transplant-free survival
Paris ⁶⁵ Corpechot	ALP <3 times ULN and ALT <2× ULN and bilirubin <1 mg/dl	1 year	Transplant-free survival
Paris II ⁶⁶ Corpechot	ALP < 1.5 times ULN and ALT < 1.5 times ULN and bilirubin < 1 mg/dl	1 year	Transplant-free survival, liver decompensation (ascites, HCC, variceal bleeding, PSE)
Rotterdam ⁶⁷ Kuiper	Normalization of bilirubin and albumin	1 year	Transplant-free survival
Toronto ⁶⁸ Kumagi	ALP < 1.67 times ULN	2 year	Histology

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; ULN: upper limit of normal; HCC: hepatocellular carcinoma; PSE: porto-systemic encephalopathy.

In the aforementioned meta-analysis of 4845 subjects, a cutoff value of ALP activity at 2 times the upper limit of normal (ULN) best forecasted subject outcome at 1 year.³³ Ten-year survival for subjects with an ALP <2 times the ULN was 84%, compared with 62% in those with higher ALP activity ($P < 0.0001$). The most specific value predicting patient survival without transplantation was a bilirubin of 1 times the ULN at one year. Ten-year survival was 86% for subjects with bilirubin levels ≤ 1.0 times the ULN, compared with 41% of those with higher levels ($P < 0.0001$). Regardless of the exact definition of biochemical response to UDCA, it is evident that normalization of liver enzymes, particularly ALP, is an eventual predictor of transplant free survival.

THERAPEUTIC AGENTS: NOVEL

Obeticholic Acid

Obeticholic acid (OCA) is a semi-synthetic analog of the primary BA CDCA, which selectively activates the nuclear hormone farnesoid X receptor (FXR). A 6-ethyl substitution on OCA enables substantial increased affinity for the FXR receptor. FXR is the key regulator of BA homeostasis and enterohepatic circulation.¹⁷ In the intestines, FXR activation modulates the expression of BA transporters by inhibiting human apical sodium BA transporter (ASBT)—the primary transporter of BA into the enterohepatic circulation.¹⁷ Activated FXR also increases expression of fibroblast growth factor (FGF-19) which, by binding to its receptor, represses both ASBT in enterocytes and CYP11 in hepatocytes (major enzyme involved in BA production).¹⁷ In hepatocytes, FXR activation limits hepatic BA accumulation by inhibiting major BA uptake system and by inducing expression of BA export pumps in the bile canicular membrane.¹⁷

OCA efficacy in PBC was examined in an international, double blind, placebo-controlled trial.³⁴ In this investigation, 59 subjects received placebo, daily doses of OCA 10 mg or 50 mg for 3 months. Compared with placebo, subjects in the OCA arms had greater improvements in AP (+0.4% vs. −38% to −45%), GGT (−3% vs. −65% to −73%), and ALT (−4% vs. −35% to −37%). The side effect profile of therapy included pruritus which occurred in 30% of patients receiving placebo, 70% of patients receiving 10 mg of OCA, and 94% of patients receiving 50 mg of OCA.

More recently, OCA (5 mg, 10 mg, or 50 mg daily) was studied to determine its efficacy and safety profile in PBC subjects without adequate response to UDCA monotherapy.³⁵ 165 subjects from 41 North American and European centers were randomized in an equal fashion to placebo or a one of three once-daily dose of OCA during which subjects continued their established dose of UDCA for 85 days. Primary endpoint was percent difference in mean ALP levels from baseline to day 85 compared with placebo and significant reductions that were met across all OCA dose groups ($P < 0.0001$). A mean decline of 21%–25% from baseline of ALP activity was noted in the OCA groups, compared to 3% in the placebo arm. In addition, there was at least a 20% decline in ALP activity in 69% of subjects treated with OCA, compared to 8% of subjects in the placebo group ($P < 0.0003$). Again, pruritus was the main side effect with increasing incidence at increasing OCA dose. ALP levels continued to decline or remained steady during a one-year open-label extension trial.

A clinical phase III study (POISE, [NCT01473524](#)) is currently ongoing comparing: OCA 10 mg daily, 5 mg daily titrated to 10 mg daily and placebo, in a randomized, double-blind fashion. Preliminary results at 1 year have report percentage of patients meeting primary endpoint (reduction in serum ALP <1.67 times ULN with a 15%

reduction from baseline levels and a normal serum bilirubin): 10% placebo group, 47%–10 mg OCA group, and 46%–5 to 10 mg OCA group (both treated groups highly significant vs. placebo arm).³⁶ Estimated completion is June 2018. A second phase III study (COBALT, NCT0230811) is currently ongoing evaluating clinical outcomes (including liver transplant and death) of PBC patients treated with OCA and is currently recruiting participants with estimated completion date of April 2023.

Fibrates

The exact immunomodulatory or anti-cholestatic mechanism of action for fibric acid derivatives is unknown. They have been shown to decrease expression of inflammatory cytokines via inhibition of NF- κ -B activation.³⁷ However, fibrates are also activators of peroxisome proliferator-activated α -receptor (PPAR α) in hepatocytes. Through activation of the PPAR α receptors, fibrates inhibit hepatic synthesis of BAs (via inhibition of CYP1A1) and uptake of BAs.³⁸ PPAR α agonists also stimulate canalicular BA transporters, including multi-drug resistance proteins, which secrete hydrophobic BA and confer protection to biliary epithelium.^{39,40}

There have been a number of small pilot studies and non-randomized trials published on fibrate therapy in UDCA non- or partial responders.^{41–44} Taken together, these studies have suggested efficacy in reducing ALP levels when fenofibrate or bezafibrate therapy is given in combination with UDCA.⁴⁵ A recent meta-analysis of 6 long-term randomized studies of 84 patients concluded that dual therapy with UDCA/fenofibrate is more potent compared to UDCA monotherapy in reducing ALP and GGT, but not pruritus in PBC.⁴⁶

A recent prospective, randomized, controlled trial compared efficacy between combination fibric acid/UDCA dual therapy vs. continued monotherapy for 27 patients on UDCA without biochemical remission.⁴⁷ At 8 years, there was significantly reduced ALP activity and Mayo risk score with bezafibrate/UDCA therapy compared to UDCA monotherapy ($P < 0.05$). Despite lower serum biochemical markers, survival was not significantly different between the treatment arms ($P = 0.057$). In addition, no significant difference in hepatocellular carcinoma was observed between the two treatment arms ($P = 0.299$). Of note, the UDCA/fenofibrate dual treatment group had significantly higher serum creatinine levels compared to the UDCA monotherapy group at 8 years of study enrollment ($P < 0.05$). Other side effects from fibrate therapy have included muscle pain,⁴⁷ reflux,⁴⁸ pruritus,⁴⁴ and elevated transaminases.⁴⁹

Currently, a phase III prospective, double-blind randomized study of bezafibrate in combination with UDCA in PBC subjects on UDCA without remission is ongoing (BEZURSO, NCT01654731). Final results are expected in December 2016.

Immunomodulatory Agents

Budesonide

Budesonide is a glucocorticoid absorbed in the small bowel with majority first pass metabolism and as a consequence, glucocorticoid receptor binding affinity much higher than that of other corticosteroids.⁵⁰ A few clinical studies have suggested that dual therapy of budesonide (6–9 mg/day) with UDCA is more efficacious in improving the hepatic biochemical indices and histology than UDCA monotherapy in PBC subjects without concurrent cirrhosis. In one study, Leuschner et al. performed a two-year prospective, controlled, double-blind study of 23 subjects undergoing dual treatment with UDCA/budesonide and 19 subjects given UDCA/placebo therapy.⁵¹ ALP activity decreased significantly compared with prior therapy levels in both treatment arms with improvement in the UDCA/budesonide significantly greater ($P < 0.05$) than in UDCA/placebo group. Interestingly, liver biopsy revealed a 30.3% improvement in histology in the combination group, while the UDCA/placebo group did not show any improvement ($P < 0.001$).

In a subsequent 3-year prospective, randomized study, 77 non-cirrhotic PBC subjects were randomized to UDCA alone (36 patients) or UDCA/budesonide (41 subjects).⁵² Hepatic biochemistries, including ALP, improved significantly in both treatment groups. Histology worsened in the UDCA monotherapy group by 20% but improved by 22% in the UDCA/Budesonide arm ($P = 0.009$). Fibrosis, determined by METAVIR score, also worsened in the UDCA monotherapy arm by 70% but improved by 25% in the combination group ($P = 0.0009$). Of note, 21% of patients treated with UDCA/budesonide had adverse effects from steroid therapy including adrenal suppression, bruising, thinning of skin, hirsutism, acne, and weight gain.

Long-term glucocorticoid therapy is rarely used due to its large side effect profile in chronic autoimmune disease. A previous pilot study evaluated safety of budesonide in PBC subjects on UDCA who did not achieve remission.⁵³ 22 PBC subjects were enrolled to undergo combination therapy with budesonide/UDCA for one year who met inclusion criteria: those on adequate UDCA for a mean of 46 months and who had not achieved biochemical response (ALP ≥ 2 times ULN). Dual therapy with Budesonide/UDCA improved ALP activity significantly after one year of therapy; however, significant decrease in bone mineral density was observed in the lumbar spine ($P < 0.001$) after the treatment period.

These aforementioned studies showed statistically significant improvement in liver biochemistries and histology with combination therapy; however, budesonide comes with side effects including osteopenia and is contraindicated in patients with underlying cirrhosis due to significantly elevated plasma levels in this setting, which may

precipitate adverse drug reactions and possible portal vein thrombosis.⁵⁴ Currently, a phase III randomized placebo-controlled trial comparing the efficacy and tolerability of a dual therapy of UDCA and budesonide with UDCA/placebo in PBC patients is underway with results expected later this year (NCT00746486).

Biologics

As innate and cell-mediated adaptive immune responses promote bile duct epithelial injury, it is likely that priming of humoral immune mechanisms occur which may further accentuate disease activity.⁵⁵ As such, there is considerable interest in the applicability of biologics in the treatment of PBC.

Rituximab is a chimeric monoclonal antibody which targets the CD20 antigen on natural and transformed B lymphocytes.⁵⁶ This monoclonal antibody specifically binds to B lymphocytes and destroys the population via humoral and cell-mediated cytotoxic mediated pathways. Not only has Rituximab been used for various malignancies (e.g. non-Hodgkin's lymphoma), it has also been found to be therapeutic in various autoimmune diseases.⁵⁷

An open label study of rituximab usage in PBC included 14 patients on UDCA (without biochemical remission) who were administered two infusions (1000 mg) 2 weeks apart and followed for 72 weeks.⁵⁶ Effective B-cell depletion was achieved in 93% (13/14) subjects but response was not sustained with rebound increase in circulating plasma B-cells after 12 weeks. However, primary outcome of at least 25% improvement in serum ALP was only observed in 3/13 (23%) patients at 6, 12, and 18 months.⁵⁶ Hence, rituximab effect on B-cell depletion shows limited value in improvement of liver biochemistries in PBC patients refractory to UDCA.

Another monoclonal antibody, Ustekinumab, is being studied in PBC patients not responding to conventional therapy. IL-12 and IL-23 are the main antigens—two cytokines paramount to Th1/Th17 signaling in PBC.⁵⁷ A phase II multicenter study evaluating the efficacy and safety of ustekinumab in 20 PBC subjects revealed no significant improvement in ALP at 12 or 28 weeks with ustekinumab therapy (NCT0138997). Other clinical trials ongoing evaluating various immunomodulatory agents in PBC refractory to UDCA include: CTLA-4 Ig (abatacept, NCT02078882) and CD40-anatagonist monoclonal antibody (FFP104, NCT02193360).

Other Experimental Therapies

There is considerable interest in the application of anti-fibrotic and stem cell therapy for PBC. Pentoxifylline is a methyl-xanthine derivative that inhibits pro-inflammatory cytokines and has potential anti-fibrotic effects. Currently, a clinical trial of pentoxifylline is being studied in a clinical trial including 20 PBC patients non-responsive to UDCA

with results pending at this time (NCT01249092). Umbilical cord mesenchymal stem cells (UC-MSC) have potential for therapy in PBC due to its potential modulatory effects of the immune system by decreasing activity of T-cells. A randomized study is currently ongoing comparing 12 weeks of treatment with UC-MSC and UDCA to 12 weeks of placebo and UDCA with initial results also pending at this time (NCT01662973). A phase I study (NCT00393185) is ongoing in PBC patients with cirrhosis and intractable pruritus unresponsive to medical therapy or with more than 50% probability of dying or needing a liver transplant.

Liver Transplantation

In patients with progressing disease who are refractory to medical management, transplantation is a viable option. Over the last two decades, while the number of liver transplants in the U.S has increased annually, total number of transplants with PBC as the indication has declined.⁵⁸ This phenomenon likely reflects beneficial effects of UDCA when used in early stages of disease.⁵⁸

While liver transplant outcomes for PBC are favorable (1- and 5-year survival: 83% and 78% respectively),⁵⁹ disease recurrence can occur. In a study of 42 transplanted patients, recurrent PBC was observed in 8% of patients after 5 years, and 22% after 10 years transplant.⁶⁰ Diagnosis of recurrence is made when all three of the following criteria are met: (1) transplantation for PBC, (2) positive AMA, and (3) allograft biopsy with compatible histology. Of note, the presence of AMA alone is not diagnostic as most patients after transplant have positive titers and these may decrease to a degree years after transplant. Earlier studies suggested that choice of calcineurin-based immunosuppression affected recurrence rate⁶¹ but findings have not been corroborated.

Recent retrospective study evaluated usage of preventative UDCA after liver transplantation and effect on recurrence. In total, 90 subjects were studied with 21% (19/90) receiving preventive UDCA. PBC recurrence was significantly lower in the UDCA-treated group. Recurrence rates were 11%, 21%, and 40% at 5, 10, and 15 years in the UDCA-preventive subjects, while recurrence rates were significantly higher at 32%, 53%, and 70% without preventive therapy. In the multivariate analysis adjusted for other confounders, UDCA treatment was the only factor affecting probability of recurrence (HR = 0.32; 95% CI: 0.11–0.91).⁶² At this time, in patients with recurrence of disease and who are non-responders to UDCA, re-transplantation may be indicated and development of novel therapies may avoid the morbidity associated with recurrent transplantation.

CONCLUSION

PBC is a progressive, autoimmune cholestatic disorder characterized by circulating AMAb and non-suppurative

cholangitis. Disease pathogenesis is multifactorial with environmental exposures triggering sustained and self-amplified innate and adaptive (cell-mediated and humoral) immune responses. These, in conjunction with bile acid toxicity, lead to progressive intrahepatic bile duct destruction and progressive cholestasis that, if left unabated, cause progression to cirrhosis. Ursodeoxycholic acid is an established therapeutic agent which retards disease progression and improves survival; however, it is not effective in achieving biochemical remission in many. New developments, including the recent approval of OCA, have ushered in a new era of therapeutics in PBC and further breakthroughs in targeting aspects of pathogenesis are anticipated.

CONFLICTS OF INTEREST

The authors have none to declare.

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