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REVIEW

Update on Emerging Treatment Options for Primary Biliary Cholangitis

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Abstract: Primary biliary cholangitis (PBC) is a rare autoimmune cholestatic liver disease that may progress to fibrosis or cirrhosis. Treatment options are currently limited. Ursodeoxycholic acid (UDCA) remains first-line therapy and has been proven to normalize serum biochemistries, halt histologic disease progression, and lead to patient survival comparable to the general population. Obeticholic acid (OCA) was recently approved as adjunct therapy in PBC patients with inadequate response or intolerance to UDCA. However, OCA has been associated with worsening pruritus in clinical studies which may limit its use in this patient population. Several studies are currently underway to address the lack of treatment options for PBC. Of these, fibrates, which have been used in Japan for over a decade, have produced promising results. Furthermore, as currently approved therapies for PBC do not address the potentially debilitating clinical symptoms of PBC such as pruritus and fatigue, supplemental therapy is often required for symptom control.

Keywords: primary biliary cholangitis, obeticholic acid, fibrate

Background

Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease characterized by destruction of small intralobular bile ducts leading to ductopenia and advanced fibrosis or cirrhosis. The diagnosis of PBC is made when at least 2 of 3 of the following are present: persistently elevated alkaline phosphatase (ALP), presence of antimitochondrial antibody (AMA), and liver biopsy demonstrating portal inflammation with destruction of small and medium-sized bile ducts.[1] As serologic markers are sufficient for diagnosis, liver biopsy is not routinely performed in this patient cohort, but may be pursued when there is a high suspicion for PBC in the absence of AMA or when concern for an overlap condition exists. AMA is a disease-specific autoantibody found in 90% to 95% of PBC patients and less than 1% of healthy individuals.[2] As many as 50% of PBC patients are also found to have antinuclear antibodies and anti-smooth muscle antibodies. The pathognomonic histologic finding of PBC is the florid duct lesion which is a focal granulomatous lesion found in less than 40% of biopsy samples from PBC patients.[3]

FDA Approved Medications

Ursodeoxycholic Acid

The widespread use of ursodeoxycholic acid (UDCA) since it was approved in 1997 by the United States Food and Drug Administration has dramatically changed the natural disease course of PBC, including decreased progression to liver

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Table 1 Approved PBC Therapies

Medication	Dose	
Ursodeoxycholic Acid (UDCA)	13–15 mg/kg/day in divided doses	
Obeticholic Acid (OCA)	In non-cirrhotic patients and in Child-Pugh class A cirrhotic patients: Start with 5 mg daily. If inadequate response after 3 months of therapy, can titrate up to maximum dose of 10 mg daily.	In Child-Pugh class B and C cirrhotic patients: 5 mg weekly

transplantation (LT) in this patient population.[4] Almost two decades passed before another medication, obeticholic acid (OCA) would be approved for use in PBC (Table 1). UDCA is a hydrophilic, synthetic bile acid which has been shown to protect cholangiocytes from inflammatory cholestatic injury induced by toxic hydrophobic bile acids such as chenodeoxycholic acid (CDCA).[5] Prior to widespread use of UDCA, approximately 49% of patients with PBC progressed to cirrhosis, compared to 13% on long-term UDCA treatment.[6] Furthermore, Prince et al showed that median patient survival was 9.3 years from time of diagnosis.[7] Multiple studies have demonstrated that when UDCA is started in early stages of PBC, patient survival is comparable to the general population.[8–10]

Standard of care for PBC includes treatment with 13–15 mg/kg/day of UDCA in divided doses. Angulo et al previously evaluated three different dose ranges for management of PBC, 5–7 mg/kg/day, 13–15 mg/kg/day, and 23–25 mg/kg/day, and found that although all three dose ranges were safe for use, the latter two were found to have significantly better improvements in ALP level and Mayo risk score compared to the lower dose.[11] Given similar treatment response between the two higher doses, the investigators recommended treatment with the standard dose of 13–15 mg/kg/day. A decade later, Lindor et al evaluated the higher dose of 28–30 mg/kg/day for treatment of patients with primary sclerosing cholangitis (PSC), and found that long-term use of the higher dose did not confer survival benefit and in fact was associated with higher rates of serious adverse events compared to placebo.[12] There is a phase 4 trial (NCT03345589) currently recruiting non-responders treated with standard dose UDCA to assess the efficacy of UDCA at 18–22 mg/kg/day in achieving biochemical remission after 6 months of treatment.

Biochemical response is typically determined after 6–12 months of continued treatment. Several criteria including Rochester I and II, Paris I and II, Toronto and the Globe score have been published to assess response, and typically require a decrease in ALP to within two times the upper limit of normal with or without concurrent normalization of bilirubin.[13–18] Unfortunately, up to 40% of patients have inadequate response to therapy.[1] Risk factors associated with decreased response rates are male gender and females younger than 45 years at time of diagnosis.[19] Inadequate or absent response to UDCA is the strongest predictor of poor outcomes in PBC patients.[20]

UDCA has also been studied for use in recurrent PBR (rPBC) after LT. Charatcharoenwitthaya et al evaluated the significance of rPBC on patient survival and the efficacy of UDCA treatment for rPBC.[21] They determined that overall rPBC was not associated with increased risk of death or re-transplantation. Furthermore, although 55% of patients treated with UDCA compared to 22% of patients not treated had normalization of their ALP and aminotransferases, there was no significant difference in the rate of histological disease progression or patient and graft survival between the two groups. It should be noted that the average dose of UDCA used in this study was 12 mg/kg/day, which is slightly lower than the standard dose of UDCA used pre-LT. Bosch et al then determined the efficacy of UDCA prophylaxis in PBC patients after LT to prevent rPBC.[22] UDCA was dosed at 10–15 mg/kg/day. They found that rPBC was significantly lower in the UDCA group compared to patients who were not started on prophylaxis (21% vs 62%, P=0.004). However, they also noted no significant improvement in long-term patient or graft survival.

Obeticholic Acid

OCA, a farnesoid X receptor (FXR) agonist, is a more potent analogue of CDCA. OCA facilitates bile acid homeostasis by suppressing de novo bile acid synthesis and increasing choleresis. In the liver, FXR agonists downregulate CYP7A1 resulting in decreased conversion of cholesterol to bile acids. In the ileum, FXR upregulates fibroblast growth factor-19 (FGF-19) which then acts on the liver to further decrease bile acid synthesis.[5,23] OCA was approved by the FDA in 2016 as an add-on therapy for patients with inadequate response to UDCA alone, and as a second-line agent for monotherapy in PBC patients intolerant to UDCA.

The drug was granted fast track designation and accelerated approval after two phase 2 trials and a phase 3 trial, the POISE study, demonstrated statistically significant outcomes with improvement in ALP levels.[24–26]

The POISE study was a 12-month trial which assessed the efficacy of OCA in normalizing biochemical outcomes in PBC patients who had inadequate response to UDCA or developed adverse events with treatment. The primary endpoints for the trial were ALP less than 1.67 times the upper limit of normal with a reduction of at least 15% from baseline, and a normal bilirubin. Patients, 93% of which were on concurrent UDCA treatment, were randomly assigned to one of the three arms, 10 mg daily, 5 mg daily with dose adjustment to 10 mg if applicable, and placebo. The group found that patients in the treatment arms were significantly more likely to achieve the primary end points than the placebo group (47%, 46%, 10%, $p \leq 0.0001$). Furthermore, response within the treatment groups was seen within 2 weeks of initiating therapy.[26] Most of the patients, 97%, went on to enter an open-label 12-month extension during which a significant proportion of patients in the treatment groups, 56% in the 5–10 mg arm and 68% in the 10 mg group, reported pruritus compared to 38% in the placebo group.[27] A total of 4% of patients in the treatment groups, one from the 5–10 mg arm and seven from the 10 mg arm, withdrew from the study due to pruritus. Similarly, in one of the phase 2 studies by Hirschfield et al demonstrating decreased levels of ALP with OCA compared to placebo in patients with incomplete response to UDCA, higher doses of OCA were associated with increased incidence and severity of pruritus with 13% of patients withdrawing from the study due to pruritus.[24] Currently, the phase 4 COBALT trial (NCT02308111) is underway to confirm clinical benefit of OCA in PBC after prolonged use. Approved dosing of OCA is dependent on the presence or absence of cirrhosis and is dosed at 5 mg daily initially in non-cirrhotic patients or in Child-Pugh class A cirrhotic patients. The dose can be titrated up to a maximum of 10 mg daily in this patient group. On the other hand, Child-Pugh class B or C cirrhotic patients are dosed at a max of 5 mg weekly. Due to incidences of inappropriate OCA dosing in cirrhotic patients leading to decompensation or acute liver failure, the FDA issued a black box warning in February 2019 highlighting the importance of correct dosing.[28] NCT03633227 is a phase 4 placebo-controlled actively recruiting trial that will be investigating the pharmacokinetics and safety profile of OCA in decompensated PBC patients over a 48-week period.

Drugs Under Investigation

Fibrates

Fibrates are peroxisome proliferator activator receptor (PPAR) agonists. There are three isoforms of PPAR: α,δ, and γ. PPAR-α is currently FDA approved for the treatment of dyslipidemia, and has been shown to exhibit anti-inflammatory and anti-thrombotic effects.[29] Furthermore, they alter bile acid metabolism by downregulating CYP7A1 and decreasing hepatic bile acid reuptake via inhibition of the basolateral transporter sodium-taurocholate-cotransporting polypeptide.[30,31] The two PPAR-α agonists that have been extensively studied in PBC are bezafibrate and fenofibrate; however, only the latter is available commercially in the US. In 1999, Kurihara et al in Japan was the first group to publish on the effect of bezafibrate for PBC. They found that bezafibrate both alone and in combination with UDCA resulted in decreased biochemical markers including ALP and bilirubin.[32] Of interest, pretreatment fatigue and itching also improved with bezafibrate treatment. This study was followed by a pilot study in the US evaluating fenofibrate use in PBC patients with inadequate response to UDCA therapy.[33] Fenofibrate at 160 mg/day was added to standard dose UDCA for 48 weeks. Median ALP levels decreased significantly ($p<0.05$) as early as 6 weeks into treatment; however, there was no change in bilirubin levels. Notable side effects included heartburn, including severe esophagitis, which led to medication discontinuation in two patients.

The BEZURSO study by Corpechot et al, a phase 3 trial, assessed the efficacy of combination treatment of standard dose UDCA with bezafibrate 400 mg daily over a 24-month period in 100 PBC patients with inadequate response to UDCA monotherapy after 6 months or more of treatment according to the Paris 2 criteria.[34] Their primary endpoint was complete normalization of ALP, bilirubin, aminotransferases, albumin, and prothrombin index. This was achieved by 31% (N=14/45) of the treatment group versus 0% (N=0/39) of the placebo group ($p<0.001$). Side effects included increased incidence of myalgia, elevated creatinine levels, and elevated amino transaminases in the treatment group compared to placebo.

Bezafibrate has been used in Japan for over a decade as a second-line agent in PBC. Honda et al recently published their retrospective data from the Japan PBC Study Group

comparing long-term outcomes using the GLOBE and UK-PBC scores in 118 patients after treatment with UDCA monotherapy for 1 year versus combination UDCA and bezafibrate therapy for another year. GLOBE score decreased from 0.508 to 0.115 ($p< 0.0001$), and 34.2% of patients were able to drop their GLOBE score to ≤0.30, suggesting comparable life expectancy to the matched general population.[35] On the other hand, although combination therapy was associated with reduced predicted risk of liver transplantation and liver-related death, actual rates of both were unchanged. Of note, a Cochrane review in 2012 demonstrated that although treatment with bezafibrate did result in improvements in certain biochemical indices of PBC, there was no statistically significant effect of intervention with bezafibrate either alone or in conjunction with UDCA on liver-related morbidity and mortality outcomes.[36]

The ENHANCE trial was a phase 3 study of seladelpar, a PPAR-δ agonist, for PBC treatment. In the prior phase 2 trial, patients with inadequate response or intolerance to UDCA were given 5 mg or 10 mg of seladelpar.[37] At week 12, patients in the 5 mg group could be dose escalated to 10 mg. ALP normalized in 25% of the 5 mg group and 29% of the 10 mg group. Unfortunately, the phase 3 trial was halted in late 2019 due to finding of interface hepatitis in concurrent trials evaluating the use of seladelpar for non-alcoholic steatohepatitis and PSC.

Elafibranor, a mixed PPAR-α and δ agonist, has recently been granted both Orphan Drug Designation and Breakthrough Therapy Designation by the FDA for treatment in PBC. In a phase 2 placebo-controlled trial (NCT03124108), the addition of elafibranor was found to significantly reduce ALP levels and improve lipid and anti-inflammatory markers. It is currently also being evaluated for the treatment of NASH in a pivotal phase 3 trial, RESOLVE-IT.

Modulator of Bile Acid Synthesis

NGM282 is a synthetic analogue of FGF-19 which modulates bile acid synthesis by downregulating the expression of CYP7A1 involved in the rate-limiting step of bile acid synthesis. In their multicenter, randomized, placebo-controlled trial, Mayo et al showed that after 28 days of treatment with NGM282, 50% of patients given the lower dose of 0.3 mg daily and 46% of patients given the higher dose of 3 mg daily were able to reach their primary endpoint of 15% or greater reduction in ALP levels compared with 7% of patients given placebo.[38] The drug was well tolerated with the most common side effect being abdominal discomfort. It should be noted, however, that overexpression of endogenous FGF-19 in mice was associated with increased development of hepatocellular carcinoma.[39] Results of the phase 2b trial evaluating the safety and efficacy of extended treatment with NGM282 are pending.

FXR Agonists

In addition to OCA, three newer FXR agonists, cilofexor (NCT02943447), tropifexor (NCT02516605), and EDP-305 (NCT03394924) are currently being investigated for use in PBC. Trauner et al recently published results from their phase 2 placebo-controlled study of cilofexor for use in patients with PSC. Patients were either treated with placebo, cilofexor 30 mg or cilofexor 100 mg daily. After 12 weeks of treatment, they observed that cilofexor at 100 mg was associated with a significant decrease in ALP ($P=0.026$), ALT ($P=0.009$), AST ($P=0.019$), and GGT ($P<0.001$) when compared to placebo. There was a trend towards improved serum biomarkers with the lower 30 mg dose of cilofexor that did not reach statistical significance. Of note, three patients in the 100 mg group discontinued the study due to side effects including pruritus, acute kidney injury, and elevated ALP. Pruritus was the most common adverse event.[40]

Immunosuppression

Although PBC is described as an autoimmune disease, immunosuppressive agents have not been shown to provide sustained efficacy as a therapeutic option. This may be due to the complex pathogenesis of PBC which involves immune-mediated inflammation as well as destruction of bile ducts and cholestasis leading to progression of inflammatory damage.

Combination therapy utilizing UDCA, budesonide and mycophenolate mofetil (MMF) have been evaluated in a small study involving 15 patients with severe PBC with interface hepatitis and not meeting diagnostic criteria for autoimmune hepatitis (AIH).[41] Patients were treated with standard-dose UDCA of 13–15mg/kg/day in divided doses, budesonide 6mg/day and MMF 1.5g/day. Fibrosis score and serum chemistries including ALT, AST and ALP normalized in 41% (N=6/14) of patients, and improved without normalization in another 47% (N=7/15).

Combination therapy with UDCA and budesonide alone has also been studied. Two prospective, randomized trials comparing budesonide and UDCA to UDCA alone and UDCA plus placebo demonstrated improved liver

enzymes and histology with addition of budesonide.[42,43] However, a third prospective trial evaluating combination budesonide and UDCA in patients without serologic improvement after 46 months of UDCA monotherapy did not show sustained biochemical improvement, and in fact, demonstrated a worsening of the Mayo risk score as well as a significant decrease in bone mass. For these reasons, the study was not extended to include a placebo-control group.[44]

Other immunomodulators such as azathioprine (AZA) and rituximab have not been proven to be efficacious for PBC management. A systematic review by Gong et al evaluating AZA for PBC identified two studies with a total of 293 patients. They found no difference in pruritus, disease progression, survival or quality of life in patients given AZA monotherapy versus placebo or no treatment.[45] Two trials evaluating the anti-CD20 monoclonal antibody rituximab for PBC did not show statistically significant or sustained improvement in serum markers for PBC after two doses of treatment in patients refractory to UDCA.[46,47]

MTX has been studied extensively in PBC, both alone and as combination therapy.[48–52] The largest placebo-controlled trial evaluating combination therapy of MTX with UDCA, the PUMPS trial, was performed by Combes and colleagues.[53] Two hundred and sixty-five patients with PBC who had been on UDCA for at least 6 months were followed for a median of 7.6 years. The investigators concluded that the addition of MTX to UDCA provided no additional clinical benefit for transplant-free survival, time to clinical deterioration, presence of varices, or histologic liver stage, and the trial was terminated early. A meta-analysis reviewing MTX in PBC including 5 trials and 455 patients, concluded that although MTX was associated with decreased ALP levels and pruritus score, it provided no statistically significant effect on need for liver transplant or mortality in this patient population.[54]

Other Agents

Several other agents have failed to show sustained effectiveness as treatment modalities in PBC. A study evaluating the effect of E6011 (NCT03092765), an anti-fractalkine monoclonal antibody, was terminated early due to lack of response after 12 weeks of treatment. In a 20-week open-label study ustekinumab, an interleukin (IL)-12/23 monoclonal antibody, was ineffective in achieving significantly decreased ALP levels in PBC patients.[55] A meta-analysis reviewing colchicine for use in PBC included 11 studies and 716 patients. The authors found that colchicine did not provide a significant clinical benefit in terms of mortality, transplant-free survival, or biochemical markers in PBC.[56]

Autoimmune Hepatitis/Primary Biliary Cholangitis Overlap Syndrome

Overlap syndromes between AIH and PBC or PSC occur in 3–17% of patients.[57] The Paris criteria are often used to identify patients with overlap syndrome involving AIH and PBC.[58] Management of AIH/PBC is determined by the predominant component of the syndrome. When PBC and AIH are equivalent, combination therapy with corticosteroids and UDCA is used. Chazouilleres et al reported their retrospective study evaluating optimal management in patients with overlap syndrome per Paris criteria with median follow-up of more than 7 years.[59] They found that combination therapy of UDCA with immunosuppression resulted in improved biochemical response and prevented further progression of fibrosis. Immunosuppression included corticosteroids with or without azathioprine as a steroid sparing agent.

Symptoms Management

Clinical symptoms of PBC include fatigue and pruritus, both of which can be debilitating and lead to decreased quality of life. Both FDA approved medications for PBC, UDCA and OCA, have no impact on management of these symptoms. Therefore, each symptom must be addressed independently. Unfortunately, treatment options are limited and liver transplantation may be the only cure for many.

Fatigue

Chronic fatigue is the most common symptom of PBC; however, this finding is non-specific and other etiologies, such as hypothyroidism, must be ruled out. Severe fatigue is associated with poor quality of life and decreased overall survival.[60] Unfortunately, randomized-controlled trials evaluating medications such as fluoxetine and modafinil have not demonstrated treatment efficacy for PBC associated fatigue.[61,62] More recently, Khanna et al published their data evaluating rituximab for fatigue.[63] Previous studies demonstrated a relationship between AMA and exercise tolerance, showing increased muscle acidosis with exercise. AMA directly affects the pyruvate dehydrogenase complex (PDC) and therefore indirectly influences the Krebs cycle.[64–66] Their aim was to determine whether reduction of AMA through B-cell depletion with rituximab, thereby decreasing the effect of AMA on cellular energy metabolism, would lead to improvements in

patient-reported fatigue and biochemical markers of disease activity. They found that the PBC-40 fatigue domain score improved in both the test and placebo arms without statistical significance. Furthermore, though they did show that patients in the rituximab group had lower levels of anti-PDC antibodies, this was not associated with improvement in PBC-40 score. Overall, they were unable to prove efficacy of rituximab for PBC fatigue management.

Pruritus

Pruritus is another common symptom of PBC, reported by up to 80% of patients. There are currently multiple medication options for PBC associated pruritus. Pruritus severity can range from mild and intermittent to constant and debilitating. Affected areas typically involve the palms of the hands and soles of the feet, and can be exacerbated by heat such as hot showers, pressure, and garments including tight-fitting clothes and wool. Cholestatic pruritus is multifactorial, involving several mechanistic pathways.

Bile Acid Resins

With cholestasis as a hallmark of PBC, patients have elevated levels of serum bile acids which can accumulate in the skin. Furthermore, bile acids are known pruritogenics that activate the G-protein coupled bile acid receptors (TGR5) and Mas-related G-protein coupled receptors (Mrgprs) involved in the neural pathways that transmit itch. As such, first-line treatment of PBC associated pruritus is bile acid resins.[67] Available formations include colestipol, colesevelam, and cholestyramine, of which the latter is the only one licensed for use for this indication. Bile acid resins can reduce the absorption of other medications such as UDCA and OCA, and therefore should not be taken within 4 hours of each other. The recommended dose is 4 g up to four times a day for a maximum dose of 16 gm daily. Symptom improvement is typically noted within 11 days of treatment. Common side effects of cholestyramine include constipation, diarrhea, and bloating. Furthermore, a common complaint of use is its unpalatability.

Rifampicin

Second-line therapy for PBC pruritus includes rifampicin and opioid antagonists. Rifampicin is a heterocyclic antibiotic that also activates the pregnane X receptor leading to decrease in autotaxin levels. The autotaxin enzyme synthesizes lysophosphatidic acid (LPA) which in turn activates TRP vanilloid 1 (TRPV1), a capsaicin receptor involved in the sensory transmission of itch.[68] Maximum dose of rifampicin is 600 mg daily. The average time to effect is 2 days. Adverse events associated with use include orange discoloration of bodily secretions, pancytopenia, renal insufficiency, gastrointestinal symptoms, and acute hepatotoxicity which can be severe. Thus, routine monitoring of liver enzymes is warranted, especially within the first 2 months of treatment initiation.

Opioid Antagonists

Cholestatic patients have been shown to have increased opioidergic tone leading to activation of the mu-opioid receptor involved in the itch pathway.[69] Naltrexone, an oral opioid antagonist has been shown through two small randomized controlled trials to be an effective option for the management of pruritus in patients with cholestatic liver disease.[70,71] Both studies demonstrated a statistically significant improvement of the visual analogue scales (VAS). Side effects associated with use include opiate withdrawal-type symptoms including dizziness, gastrointestinal symptoms and headaches which typically subsided after 2–3 days of treatment. Naltrexone is started at 12.5 mg orally and titrated to effect with maximal dose of 50 mg daily. Other opioid antagonists such as naloxone and nalmefene have been studied and demonstrated symptom improvement in PBC. However, their use is limited in that naloxone is administered parenterally and oral nalmefene is not currently available in the United States.[72,73] Of note, patients with chronic pain must be monitored closely as their pain may be exacerbated with use.

Selective Serotonin Reuptake Inhibitors

Descending serotonergic pathways from the medulla are thought to tonically facilitate itch. As such, sertraline has been shown in a small retrospective study to statistically improve pruritus based on VAS in a dose-dependent fashion up to 100 mg daily. Further, dose escalation was not associated with symptom improvement. Thus, the optimal dose of sertraline is 75 mg to 100 mg daily.[74] Side effects of use include dizziness and GI symptoms.

Conclusion

PBC is a rare and progressive cholestatic liver disease. Although several treatment options have been investigated, UDCA remains first-line therapy and has proven efficacious in normalizing serum biochemistries and halting the progression of fibrosis leading to longer transplant-free survival. Though OCA was FDA approved for combination therapy in patients with inadequate response to UDCA, the

significant side effect of pruritus may limit its use in patients already afflicted with severe symptoms. The pipeline remains promising as multiple trials are underway to address patients with inadequate or non-response to therapy with UDCA.

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