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Literature Review

Emerging Therapies in Primary Biliary Cholangitis (PBC). A Comprehensive Review of the Current Trials

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Abstract

Primary biliary cholangitis (PBC) represents a quite rare liver disease. The therapeutic approaches are limited and include the first-line treatment with ursodeoxycholic acid (UDCA). In this review, we summarize and review the emerging therapies for PBC. Ten phase-2 and phase-3 randomized control trials on PBC treatment with 992 subjects have provided data concerning biochemical responses of treatment. 35% of the patients with PBC have an inadequate biochemical response after one year of UDCA. Novel therapies including FXR agonists, PPARs agonists, and Immunomodulators are emerging. .

Keywords: *Primary Biliary Cholangitis (PBC); Antimitochondrial Antibodies (AMA); Ursodeoxy-Cholic Acid (UDCA); Obeticholic Acid (OCA); Peroxisome Proliferator-Activated Receptor (PPAR); Farnesoid X Receptor (FXR)*

Introduction

Primary biliary cholangitis (PBC), formerly referred to as primary biliary cirrhosis, is an autoimmune chronic liver disease of unknown origin characterized by a T cell-mediated inflammation of intrahepatic bile ducts, which eventually results in progressive intrahepatic cholestasis leading to cirrhosis [1]. Some evidence supports the interaction of microbial and xenobiotic environmental factors and cellular pathways as possible pathogenetic mechanisms [2,3]. Although an infectious etiology for triggering PBC has been suspected, a specific etiologic agent such as bacteria, viruses, or toxins has not been identified. It has been hypothesized that PBC patients are somewhat "hyper-responsive" to IgM production, and this phenomenon may reflect how microorganisms interact with the immune system [4]. As the family prevalence of PBC ranges between 1 - 7.1%, a genetic susceptibility may be hypnotized [5,6]. Moreover, PBC has a significant predominance in women between 30 and 60 years old, with the disease ratio among females to males to be 10:1, indicating that the X chromosome is involved in some way to immunological tolerance [7].

Although PBC represents a quite rare liver disease, the overall global rates of PBC incidence and prevalence are constantly increasing, which is reasonable considering that studies over the last 25 years have been of poor quality and reliability due to limited sample [8]. According to a 12-year study of the Fibrotic Liver Disease Consortium study published in 2018, an increase of 72% is recorded in prevalence

among the female population of the USA, while the corresponding increase in men is estimated at more than 114% [9]. Recent research in Asian territory confirmed a notable increase in epidemiological rates of PBC in China over the last 16 years with simultaneous alarming mortality [10]. Therefore, it is accepted that PBC has a significant geographical heterogeneity in the annual prevalence and incidence rates. The highest prevalence rates are recorded in the USA with 402 cases per million inhabitants, Greece with 365 cases per million inhabitants, and England with 240 cases per million inhabitants [11,12]. On the other hand, Australia's lowest rates have been reported with only 19 cases per million and Canada with 22 cases [12].

European Association for the Study of the Liver (EASL) recommends that in adult patients with cholestasis and no likelihood of systemic disease, a diagnosis of PBC can be made based on elevated alkaline phosphatase (AP) levels and the presence of antimitochondrial antibodies (AMA) at a titer > 1:40 [13]. According to the American Association for the Study of Liver Diseases (AASLD), the diagnosis of PBC is established when at least two of the following three criteria are present: 1) Biochemical evidence of cholestasis based on AP elevation, 2) presence of AMA or other PBC-specific autoantibodies (sp100 or gp210) and 3) histologic evidence of nonsuppurative destructive cholangitis and destruction of inter-lobular bile ducts [14]. AMA is the most specific serological marker detectable in the overwhelming majority of patients. However, histological assessment better reflects the disease's stage [12]. Patients with PBC experience a wide range of symptoms that cause a significant impact on their quality of life, including pruritus, fatigue, or bone disease [15]. The prognosis of PBC has been improved due to the advent of new diagnostic and therapeutic methods [16]. However, the therapeutic approach is limited and includes the 1st line treatment with ursodeoxycholic acid (UDCA), approved since 1997 by the United States Food and Drug Administration and is considered the backbone of the pharmaco-logic therapy for all patients with PBC.

UDCA is a bile acid that leads to a reduction in cholesterol in biliary fluid primarily by dispersing the cholesterol and forming a liquid-crystal phase. In general, patients treated with UDCA who were initially diagnosed with mild disease and achieve a biochemical response to UDCA have a better prognosis than those with advanced fibrosis or cirrhosis or those who fail to achieve a complete biochemical response to UDCA. The median survival of patients whose therapy is ineffective ranges from 5 to 8 years from the onset of the symptoms, while the terminal phase of PBC may lead to ascites, liver transplantation, gastrointestinal bleeding, and death [17]. UDCA achieves the amelioration of the liver's histological characteristics and reduces the need for liver transplantation. Most early-stage UDCA-treated PBC patients have an expected survival similar to the general population [8]. The most frequent side effect during treatment in clinical trials was diarrhea, while the exacerbation of pruritus was another reported adverse event [18].

Obeticholic acid (OCA) has recently been recognized as a 2nd line treatment for PBC patients with inadequate response or intolerance to UDCA [19,20].

Other investigational therapies include unlicensed agents such as corticosteroids, fibrates, peroxisome proliferator-activated receptor (PPAR)-alpha and -gamma agonists, and immunomodulating agents and have mainly been used as "salvage" therapies in patients with inadequate response or intolerance to UDCA/OCA [9].

Aim of the Study

This review aims to provide information regarding the promising therapeutic tools for PBC, including the current pipeline of the main medicinal products evaluated in clinical trials.

Materials and Methods

Search strategy

A search has been performed on www.clinicaltrialsregister.eu, www.clinicaltrials.gov and on International Clinical Trials Registry Platform databases maintained by the EMA, FDA, and WHO, respectively.

Inclusion criteria

Randomized controlled trials (RCTs), phase IV, III, II, I of assessing medicinal products in patients with PBC were selected. The main characteristics of the trials, as well as the primary outcomes, were extracted.

Results

Study selection and characteristics

Twenty-five (25) records were initially identified. The clinical trials in Phase 2 pre-vail over the others with a rate of 57%. The phase 3 studies follow with a rate of 26%, and the rest of the studies are divided into phase 4 with 4%, phase 1 with 4%, and pre-clinical phase with 9%. Thus, ten phase-2 and phase-3 randomized control trials on PBC treatment with a total of 992 subjects have provided data concerning AP changes and bio-chemical responses of treatment (Table 1).

Drug	Mechanism of Action	Phase	N	Duration	Primary outcome	Common AEs	Clinical Trial Number
OCA 5-10, 10 mg	FXR agonist	3	217	1-5 years	Percentage of participants at month 12 with AP < 1.67 x ULN and total bilirubin ≤ ULN and AP decrease of ≥ 15% from baseline: 46% in 5-10 mg group, 47% in 10 mg group, 10% in placebo group	Pruritus: 56% in 5-10 mg group, 68% in 10 mg group, 38% in placebo group	NCT01473524 (POISE)
EDP-305, dose 1, dose 2	FXR agonist	2	68	12 weeks	Proportion of subjects with at least 20% reduction in ALP from pre-treatment value or normalization of ALP at Week 12: not achieved	pruritus, gastrointestinal-related symptoms	NCT03394924 (INTERPID)
Tropifexor 0.03, 0.06, 0.09, 0.15 mg	FXR agonist	2	61	28 days-12 weeks	The fold change in serum gamma-glutamyl transferase (GGT) from baseline to day 28: was achieved in all groups except the one of 0.03 mg dose	Pruritus: 44% in the 0.03 mg group and 53% in the 0.06 mg group	NCT02516605
Cilofexor 100, 30 mg	FXR agonist	2	71	12 weeks	Reduction in AP ≥25% from baseline to week12 has been observed in 17% on CILO 100 mg, 18% on 30 mg, and 0% on placebo	pruritus leading to treatment discontinuation occurred in 7% of patients on CILO 100 mg vs. none treated with CILO 30 mg or placebo	NCT02943447
Elafibranor 80, 120 mg	PPARα/δ agonist	2	45	52-104 weeks	Response to treatment defined as AP < 1.67 xULN and total bilirubin ≤ ULN and AP decrease ≥ 15 percent: 67% patients in the Elafibranor-80 mg group and 79% patients in the Elafibranor-120 mg group, versus 6.7% patients in the placebo group	All possible drug-related, non-serious adverse events were mild to moderate	NCT03124108

Seladelpar 2, 5, 10 mg	PPARδ agonist	2	119	12-26 weeks	Preliminary data from this study concerning 71 cirrhotic patients has been shown a reduction at week 26 from baseline AP of 30% and 38% in the 5 and 10 mg groups, respectively	Seladelpar was generally safe and well-tolerated, with no de-compensations reported	NCT02955602
Bezafibrate 400 mg	PPARα,δ,γ agonist/FXR agonist	3	100	24 months	Percentage of patients with a complete biochemical response: occurred in 31%, while normal levels of AP were observed in 67%.	The most ordinary adverse event caused by fibrates was muscle pain, while the possibility of rhabdomyolysis is relatively low	NCT01654731 (BEZURSO)
Budesonide 9 mg	Glucocortical steroid	3	62	36 months	Primary efficacy was defined as an improvement of liver histology concerning inflammation and no progression of fibrosis: Budesonide add-on therapy was not associated with improved liver histology in patients with PBC and insufficient response to UDCA	Arthralgia, osteopenia, cataract(s), muscle spasms, hypertension, dyspepsia, weight increase, abdominal pain, peripheral edema, and blood cortisol decrease were noticeably more frequent in the budesonide group than in the placebo group	NCT00746486
Linerixibat 20, 90, 180 mg	ASBT inhibitor	2	147	12 week	Mean change from baseline at week 16 in the Mean Worst Daily Itch Score: three Linerixibat groups, 40 mg and 90mg twice daily, and 180mg daily, demonstrated significant improvement in itch vs. placebo over the 12-week treatment period	The most notable side effect that reported was diarrhea and abdominal pain	NCT02966834
Setanaxib 400, 800 mg	NADPH oxidase NOX1/NOX4 inhibitor	2	102	24 weeks	The percent change in serum GGT: 32%	All doses tested were well-tolerated, with no safety signal compared to the placebo	NCT03226067

Table 1: *Clinical trials: Phase 2 and 3 with published primary endpoints results.*

PBC trials studying farnesoid X receptor (FXR) agonists

FXR was identified as a receptor of bile acid. FXR plays a crucial role in the secretion and the regulation of bile acid synthesis. In particular, FXR translocates to the cell nucleus, creates a bipartite, and attaches to hormone response elements on DNA. One of the functions

of FXR activation is the suppression of cholesterol 7 alpha-hydroxylase (CYP7A1), function as limiting enzyme in bile acid synthesis from cholesterol. FXR is attached indirectly to the CYP7A1 promoter. In contrast, FXR causes the expression of a heterodimer partner (SHP), which then functions to inhibit transcription of the CYP7A1 gene. In this way, an adverse feedback pathway is established in which the synthesis of bile acids is inhibited when cellular levels are already elevated. The current knowledge of systemic FXR biology provides pharmacological aspects of FXR modulation for therapeutic strategies and innovative drug development for cholestatic diseases. OCA has been the first FXR agonist, which has been approved for the treatment of PBC. OCA can be used either in combination with UDCA or as monotherapy in UDCA refractory cases. However, other trials involving OCA are on the way.

NCT01473524

In this phase-3 study (POISE), OCA is used as a first-in-class agonist that selectively binds to the FXR. OCA functions, directly and in-directly, to quell bile acid production in the liver and increase bile flow due to reduced liver exposure to dangerously toxic levels of bile ac-ids. The study assigned 217 patients who had an inadequate response to UDCA or found the side effects of UDCA unacceptable and included 2 phases: a 12-month randomized, double-blind (DB), placebo-controlled, parallel-group phase, followed by a long-term safety extension of up to 5 years. Patients received OCA at a dose of 10 mg (the 10-mg group), OCA at 5 mg with adjustment to 10 mg if applicable (the 5-10-mg group), or placebo. The primary endpoint, which was an AP of less than 1.67 times the upper limit of the normal (ULN) range, with a reduction of at least 15% from baseline with normal total bilirubin levels, was achieved in 46% of the 5-10-mg group and 47% of the 10-mg group. Both arms resulted in decreases from baseline in AP and total bilirubin levels that differed significantly from the placebo group (10%; $P<0.001$ for both comparisons) [21,22]. However, pruritus was the most common adverse event that occurred dur-ing the double-blind phase across all groups, with a higher incidence reported in the 5–10-mg group (56%) and the 10-mg group (68%) than in the placebo group (38%) [21].

NCT04278820

TQA3526 is a modified bile acid and FXR agonist under investigation in a phase-2, randomized, double-blind, placebo-controlled study concerning the treatment of naive or previously treated 130 PBC patients. The study's primary outcome is the reduction of AP and has no results have been posted until now.

NCT03394924

EDP-305 is a novel and highly potent FXR agonist. The INTREPID study was a 12-week, randomized, double-blind, placebo-controlled phase-2 study evaluating the safety, tolerability, pharmacokinetics, and efficacy of EDP-305 in 68 subjects with PBC with or without an inadequate response to UDCA. The study consisted of two treatment arms. The study's primary endpoint was to evaluate the proportion of subjects with at least a 20% reduction in AP from pre-treatment value or normalization at week 12. The EDP-305 was safe in the ma-jority of the subjects with PBC; the most common adverse effects included pruritus, gastrointestinal-related symptoms (abdominal pain, diarrhea, gastroesophageal reflux), headache, and insomnia. However, the study did not meet the primary endpoint in sub-jects with PBC, as defined by at least a 20% reduction in AP in the intent-to-treat set analysis.

NCT02516605

A multi-part, double-blind phase-2 study with 61 participants has assessed the safety, tolerability, and efficacy of Tropifexor (LJN452) in PBC patients. The participants were di-vided into five arms-groups with diverse posology of Tropifexor such as 0.03-0.06-0.09-0.15 mg and the placebo daily for 28 days. The primary outcome was the fold change in serum gamma-glutamyl transferase (GGT) from baseline to day 28. The most notable side effect was pruritus, reported by 12% in the placebo group, 44% in the 0.03 mg group, and 53% in the 0.06 mg group. Thus, except that for the 0.03 mg dosage, all groups achieved the study's primary outcome.

NCT02943447

A phase-2 study was performed to evaluate the safety, tolerability, and efficacy of Cilofexor (CILO) in adults with PBC without cirrhosis. The study enrolled 71 participants randomized in a 2:2:1 ratio to receive CILO 100 mg, CILO 30 mg, or placebo orally once daily for 12 weeks. The primary outcome was defined as the percentage of participants experiencing Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs). However, a reduction in AP ≥ 25% from baseline to week 12 was observed in 17% on CILO 100 mg, 18% on 30 mg, and 0% on placebo. In addition, pruritus leading to treatment discontinuation occurred in 7% of patients on CILO 100 mg vs. none treated with CILO 30 mg or placebo [23]. Moreover, the study was terminated be-cause of the availability of alternative therapies for PBC.

PBC trials studying PPARs receptor agonist

The peroxisome proliferators mediate interaction with activation of PPARs receptors by regulating gene transcription. PPARs are a group of nuclear receptor family. They are dis-tributed in three receptor isoforms designated as PPAR-α, PPAR-δ, and PPAR-γ, the former isoform most strongly expressed in the liver. PPARs stimulate the transcription and protein expression of multidrug resistance protein 3 (MDR3) by binding response elements in the MDR3 promoter and increasing the biliary excretion of phosphatidylcholine [24]. The drugs belonging to PPARs receptor agonists used in PBC treatment are Bezafibrate, Elafibranor, Saroglitazar, and Seladelpar.

NCT01654731

The most promising investigational treatments include fibrates (Fenofibrate and Bezafibrate). Their mechanism of action consists in the induction of lipoprotein lipolysis, induction of hepatic fatty acid (FA) uptake and reduction of hepatic triglyceride production, in-creased removal of LDL particles, reduction in neutral lipid (cholesteryl ester and triglyceride), and increase in HDL production and stimulation of reverse cholesterol transport [25]. Fibrate derivatives exert their effects mainly through PPAR-α agonistic property. Bezafibrate used as a ligand of PPARs and is a dual PPARs/PXR agonist. Acting as a PXR agonist inhibits CYP7A1 and stimulates CYP3A4, MDR1, and MRP2 [26]. BEZURSO in phase-3 study is a multicenter, randomized, double-blind placebo-controlled trial of Bezafibrate for PBC treatment with 100 participants. The subjects follow a posology strategic scheme with 400 mg/day of Bezafibrate. The primary outcomes measure the per-centage of patients with complete biochemical responses and standardization of hepatic biochemical tests in 24 months. The primary outcome occurred in 31% of the patients as-signed to Bezafibrate, while normal levels of AP were observed in 67% of the patients. Overall, 424 adverse events were reported in 88 patients (49% in the Bezafibrate group and 51% in the placebo group). Creatinine levels increased 5% in the Bezafibrate group and decreased 3% in the placebo group. Myalgia was reported in 20% of the patients in the Bezafibrate group and 10% in the placebo group. The most ordinary adverse event caused by fibrates was muscle pain, while the possibility of rhabdomyolysis is relatively low, but it cannot be excluded [27].

NCT04526665

Elafibranor is an agonist of the PPARα and PPARδ, which improves insulin sensitivity, glucose homeostasis, and lipid metabolism and reduces inflammation. This study of Elafibranor is a double-blind, randomized, placebo-controlled phase-3 study and open-label long-term extension to evaluate the efficacy and safety in patients with PBC and inadequate response or intolerance to UDCA (ELATIVE). The enrollment of this study included 150 participants and has no results posted. The primary outcome measure is the effect of Elafibranor (80 mg/day) on cholestasis with a time frame from baseline to 52 weeks of treatment. The study's primary outcome was defined as AP < 1.67 x ULN and total bilirubin ≤ ULN and AP decrease ≥ 15 percent. The therapy with Elafibranor could be considered well-tolerated since not a single death was reported in the completed study NCT03124108 [28]. The drug-related -non-dangerous side effects that the participants mentioned contained fatigue, headache, diarrhea, and nausea. At the same time, the most severe adverse cases happened

mainly to patients who had received the dose of 120mg and included ischemic stroke, high levels of aminotransferases that may suggest auto-immune hepatitis, and myasthenia gravis.

NCT03124108

Elafibranor has been evaluated in another randomized, double-blind, placebo-controlled, phase 2 study. The study enrolled 45 participants who received Elafibranor 80 mg, or Elafibranor 120 mg or placebo for 12 weeks. The composite endpoint of AP≤1.67-fold the ULN, decrease of AP > 15%, and total bilirubin below the ULN was achieved in 67% patients in the Elafibranor-80 mg group and 79% patients in the Elafibranor-120 mg group, versus 6.7% patients in the placebo group. At the same time, it was safe and well-tolerated [28].

NCT04620733

RESPONSE is an interventional placebo-controlled, randomized, phase 3 study to evaluate the efficacy and safety of Seladelpar in patients with PBC and an inadequate response or intolerance to UDCA with 180 participants. The Seladelpar is a potent active - PPARδ agonist, located in various cell types such as hepatocytes, cholangiocytes, Kupffer cells, and stellate cells. Data supports its effect on regulating genes involved in bile acids syn-thesis, inflammation, and fibrosis. Inflammation and destruction of the intrahepatic bile bodies may provoke progression to fibrosis, cirrhosis, and liver failure [29]. The subjects of the RESPONSE study are divided into three arms according to posology 5 mg, 10 mg, and placebo for a treatment duration of up to 12 months. The expected primary outcome measures are the AP < 1.67× ULN and the total bilirubin levels ≤ 1.0× ULN, but still, has no results were posted.

NCT02955602

Seladelpar has been evaluated in another open-label, randomized, phase 2 study with 119 participants. The primary outcome was to assess the safety and efficacy of Seladelpar 2 mg, 5 mg, and 10 mg over eight weeks of treatment in patients with PBC and an inadequate response to UDCA intolerance. Although there are no posted results, preliminary data from this study concerning 71 cirrhotic patients has been shown a reduction at week 26 from baseline AP of 30% and 38% in the 5 and 10 mg groups, respectively. In addition, Seladelpar was generally safe and well-tolerated, with no decompensations reported [30].

NCT03602560

To evaluate the safety and effect on cholestasis of two Seladelpar regimens (5 mg/day titrated to 10 mg/day and 10 mg/day) compared to placebo, a 52-week placebo-controlled, randomized, phase-3 study in 240 participants with PBC and an inadequate response to or intolerance to UDCA has been conducted [31]. There are no posted results. The primary outcome was AP level < 1.67 x the ULN with at least a 15% decrease from baseline and a normal total bilirubin level after 52 weeks. As the company announced, Seladelpar achieved the primary composite outcome with high statistical significance in 78.2% of patients in the 10 mg group and 57.1% in the 5 mg group compared to 12.5% on placebo after three months ($p < 0.0001$). Moreover, Seladelpar demonstrated a robust and dose-dependent reduction in pruritus after just three months of treatment with a favorable safety and tolerability profile [32].

NCT03112681

The safety, tolerability, and efficacy of Saroglitazar in patients with PBC has been assessed in a prospective, multicenter, randomized, double-blind, placebo-controlled phase-2 study (EPICS) with 37 participants, divided into 3 arms-groups with posology characteristics of 2 mg, 4 mg, and the placebo. The main results depend on primary outcomes on AP levels in patients with PBC after a 16-week treatment duration and has no results posted. Saroglitazar is a dual activator of PPRa and PPRγ. The action of Saroglitazar causes lowers high blood triglycerides and improves insulin resistance. On the other hand, adverse effects like weight gain and edema, identified with similar molecules like the glitazone class of drugs [33].

PBC trials using immunomodulators

NCT02135536

NGM282 (Aldafermin) is an engineered version of the human hormone fibroblast growth factor 19 (FGF19). FGF19 has been recognized as an essential role as a hormone produced in the ileum in response to bile acid absorption; it regulates new bile acid synthesis and affects glucose and lipid metabolism. Aldafermin for the treatment in patients with PBC has been evaluated in a 28-day multi-center, randomized, double-blind phase-2 trial with an estimated enrollment of 150 participants. The change in plasma levels of AP from baseline to week 12 was the study's primary outcome. Most adverse events were grade 1 to grade 2 in severity, with gastrointestinal disorders more frequent in the treatment group vs. placebo [34].

NCT03742973

A phase-2 study of Baricitinib, a Janus kinase (JAK) Inhibitor, investigates its efficacy in patients with PBC who cannot take the first-line treatment UCDA or have an inadequate response. Unfortunately, the study was terminated due to enrollment futility.

NCT03521297

Another approach includes probiotics, which increase bile acid synthesis and metabolism in both mice and humans. This ongoing phase-2 study evaluates the efficacy of these drugs combined with UDCA for six months in patients with inadequate response in monotherapy with UCDA.

NCT04604652

PRONTO-PBC is a phase-2 study with the molecule HTD1801 (BUDCA) in 30 adult sub-jects with PBC who have an inadequate response on therapy with UDCA. The mechanism of action of this molecule is as MP-activated protein kinase (AMPK) activator. AMP-activated protein kinase (AMPK) phosphorylates proteins to regulate through a wide range of biochemical components such as fatty acid, cholesterol, carbohydrate, and amino acids severe metabolic pathways of autophagy, mitochondrial function, and cell growth.

Other PBC trials

NCT00746486

Another double-blind, randomized, placebo-controlled phase-3 study involving 62 participants aimed to compare the efficacy and tolerability of combination therapy with UDCA plus Budesonide vs. UDCA plus placebo in PBC treatment. Budesonide is a corticosteroid with potent glucocorticoid activity, which leads to the synthesis of anti-inflammatory proteins and may contribute to AP levels amelioration in PBC patients. The study was terminated on the recommendation of the IDMC (Independent Data Monitoring Committee) after a planned interim analysis [35]. Budesonide add-on therapy was not associated with improved liver histology in patients with PBC and insufficient response to UDCA. However, the proportion of patients with AP < 1.67×ULN, a ≥ 15% de-crease in AP and normal bilirubin was higher in the budesonide group than in the placebo group at 12, 24, and 36 months ($p < 0.05$, each), while 35% of Budesonide -treated patients achieved normalization of AP levels. Arthralgia, osteopenia, cataract(s), muscle spasms, hypertension, dyspepsia, weight increase, abdominal pain, peripheral edema, and blood cortisol decrease were noticeably more frequent in the budesonide group than in the placebo group [1].

NCT03954327

A different and interesting approach for treating PBC patients unresponsive to UDCA constitutes a placebo-controlled, double-blind, randomized controlled trial with 12 months of Tenofovir Disoproxil and Raltegravir as combination antiretroviral therapy (cART). The study enrolled 60 participants with intervention posology of Emtricitabine 200 mg/Tenofovir Disoproxil 300 mg by mouth once per day plus Raltegravir 600 mg two tablets by mouth once per day. The placebo comparators are two capsules identical to Raltegravir and one capsule identical to Emtricitabine with no active ingredients per os once per day. The primary outcome of this phase-2 study is the moderation of AP after the conclusion of 12 months of treatment and has no results posted.

NCT02966834

This phase-2 study is being conducted to evaluate the efficacy, safety, and tolerability of Linerixibat administration for the treatment of pruritus in participants with PBC (GLIM-MER). Linerixibat is a novel molecule that inhibits the Apical Sodium-dependent Bile acid Transporter (ASBT), by blocking the resorption of bile acids in the small intestine, Linerixibat reduces pruritic bile acids in circulation. In the GLIMMER study, the outcomes are quite promising as the amelioration of quality of life and the reduction of the severity of itchiness in patients who have received the drug is statistically significant compared to the placebo. The actual enrollment of this study is 147 participants divided into five arms according to experimental posology. The experimental posology for each subject was 20 mg, 90 mg (once a daily or twice), 180 mg and the placebo. Three Linerixibat groups, 40 mg, 90 mg twice daily, and 180 mg daily, demonstrated significant improvement in itch vs. placebo over the 12-week treatment period (N = 22, 22, 24, respectively, vs. placebo N = 36, $p = 0.011$, 0.037, 0.042, respectively). In addition, the treatment with Linerixibat is well-tolerated, while the most notable side effect reported was diarrhea and abdominal pain [36].

NCT03226067

The study assessed the safety and efficacy of GKT13783 (Setanaxib) in patients with PBC who take a stable UDCA dose and persistently high AP levels. This double-blind, randomized, placebo-controlled, multicenter, parallel-group phase-2 trial with 102 subjects randomized and allocated to placebo or one of the two active treatment arms, according to a 1:1:1 randomization ratio for 24 weeks. The primary outcome was the percent change in serum GGT. GKT137831 is an NADPH oxidase (NOX) inhibitor. NOX produces superoxide, hydrogen peroxide, and others, called free radicals, and are toxic if they are present in excess amounts. The study drug blocks the activity of a subset of NOX enzymes which could be involved in the progression of PBC. All doses tested were well-tolerated, with no safety signal compared to placebo. Setanaxib achieved clinically meaningful reductions in liver stiffness, a statistically significant reduction in GGT ($p < 0.002$), and AP ($p < 0.001$) over the 24-week treatment period but did not achieve statistical significance in the reduction of GGT at week 24. However, after post-hoc analysis correcting a non-normal distribution of GGT values, the statistical significance of $p = 0.02$ is achieved for the primary-endpoint, leading to a reduction of GGT of 32% [37].

Conclusion

PBC represents a challenging to treat disease, as approximately 35% of patients have an inadequate biochemical response after one year of UDCA. Chronic impairment of bile flow leads to portal and parenchymal inflammation and eventually to cirrhosis. On the other hand, the management of symptoms of cholestasis is another therapeutic challenge in these patients. Thus, novel therapies for PBC are emerging. The pipeline product pro-files are high hopes, and soon, we expect many new drugs for the PBC treatment. In recent years new pharmacological studies have moved therapy from UDCA to another licensed treatment with OCA. At the same time, further data becomes available, including novel agents like FXR agonists, PPARs agonists, fibrates, and maybe immunomodulators. Although most of these new drugs are still in clinical trials and do not have data from daily clinical practice, they appear to contribute to the effectiveness of treatment,

especially with co-administration with UDCA. The most promising investigational treatments so far include FXR agonists and fibrates. An important issue for the authorization of new medicines is the quality of life of patients. In the case of PBC, the expected results of the clinical trials indicate that the new molecules may help to improve the quality of life of patients. However, it remains to be confirmed that the remaining necessary data are also valuable so that we have a clear horizon for the future opportunities of patients with PBC.

Author Contributions

Authors contributed equally to this manuscript. K.P. wrote, edited, and conceived the manuscript. A.F. wrote, edited and conceived the manuscript. N.P. wrote, edited, and conceived the manuscript. C.K. wrote, edited, and conceived the manuscript. M.D. wrote, edited, and conceived the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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