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Review Article

UDCA: AN ESTABLISHED MANAGEMENT FOR PRIMARY BILIARY CHOLANGITIS AND A NEED FOR MORE ALTERNATIVE THERAPEUTIC REMEDIES. A REVIEW

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ABSTRACT

Primary Biliary Cholangitis (PBC) is a chronic autoimmune liver disease characterized by progressive destruction of intrahepatic bile ducts, leading to cholestasis, fibrosis, and potentially liver failure. Ursodeoxycholic acid (UDCA) remains the first-line therapy and has significantly improved transplant-free survival. However, up to 40% of patients exhibit an incomplete biochemical response or intolerance to UDCA, necessitating second-line or adjunctive treatments. Obeticholic acid (OCA), a potent FXR agonist, is the first approved second-line agent, demonstrating efficacy in UDCA non-responders, though concerns regarding tolerability and safety in advanced liver disease persist. Besides OCA, other potential treatments are being actively studied, including fibrates, PPAR agonists (bezafibrate, seladelpar, elafibranor, saroglitazar) and FXR agonists (tropifexor, cilofexor). Agents in development include IBAT inhibitors, IL-31 blockade, and NOX inhibitor to improve pruritus and fibrosis symptoms. There are also experimental methods which are tried, like mesenchymal stem cell therapy and FGF19 analogs. This review focuses on a critical review of current and experimental treatment, risk-stratification tools, and criteria of treatment response, representing the evolving nature of PBC management dynamic and the necessity to employ personalized, mechanism-based treatment strategies.

Keywords: Biliary Cholangitis, Second line, Ursodeoxycholic Acid (UDCA), Obeticholic Acid, Fibrates, therapeutic advances, investigational therapies.

INTRODUCTION

Primary Biliary Cholangitis (PBC) is a chronic, progressive autoimmune cholestatic liver disease that predominantly affects middle-aged women, typically between the ages of 40 and 60 [1]. Its characteristic trait is an immunologic destruction of small intrahepatic bile ducts followed by a cholestasis and a diffuse hepatic inflammation, progressive fibrosis, finally cirrhosis in case of untreated conditions [2]. The pooled global incidence and prevalence of PBC were 1.76 and 14.60 per 100 000 persons, respectively [1,3].

The disease is strongly associated with the presence of antimitochondrial antibodies (AMA), which are detectable in approximately 90–95% of affected individuals and serve as a key diagnostic marker [4]. Diagnosis is usually established through a combination of biochemical evidence of cholestasis (notably elevated alkaline phosphatase), serological positivity for AMA, and, when needed, histopathological evaluation via liver biopsy to confirm or exclude overlapping conditions [5].

The pathogenesis of PBC involves a complex interplay of genetic predisposition, environmental triggers, and dysregulation of both innate and adaptive immune responses. Environmental exposures such as recurrent urinary tract infections, cigarette smoking, cosmetic products, and xenobiotics have been implicated in initiating or exacerbating the autoimmune cascade [6]. New insights of disease progression are the intrahepatic accumulation of cytotoxic bile acids, compounded by impaired bicarbonate secretion by biliary epithelial cells, which further damages cholangiocytes and promotes ductopenia [7].

In the past, PBC used to be the most common leading cause of liver transplantation due to the persistent nature of the disease. Nevertheless, with the implementation of ursodeoxycholic acid (UDCA) the condition has changed dramatically [8]. UDCA is the proven first-line treatment, a hydrophilic bile acid, which can raise the biochemical markers, stall the histological progression, and decrease the demand of liver transplantations [9]. However, UDCA is incomplete or a non-responder to about 30 to 40 percent of patients that places them at persistent risk of disease development and disorders including portal hypertension, osteoporosis, hepatocellular carcinoma [10].

This gap in treatment in the recent years has spurred the interest on alternative and adjunct therapies. The investigational medicine and second-line agents such as obeticholic acid (OCA), bezafibrate, seladelpar and elafibranor have come up and are promising agents since they present novel opportunities to modulate the disease and achieve better patient outcomes [11].

This systematic review seeks to establish an overall conclusion concerning the established place of UDCA in the management of PBC and critically support the efficacy, safety, and mechanistic profile of the new cost-effective therapeutic options available in patients that do not respond adequately to UDCA.

Ursodeoxycholic Acid: Established First-Line Therapy:

Mechanism of Action and Clinical Efficacy:

Ursodeoxycholic acid (UDCA) remains the cornerstone of treatment for Primary Biliary Cholangitis

(PBC). It is a synthetic, hydrophilic bile acid administered orally at a standard dose of 10–15 mg/kg/day [12]. UDCA exerts multiple therapeutic effects through several proposed mechanisms which are shown in figure 01 [13].

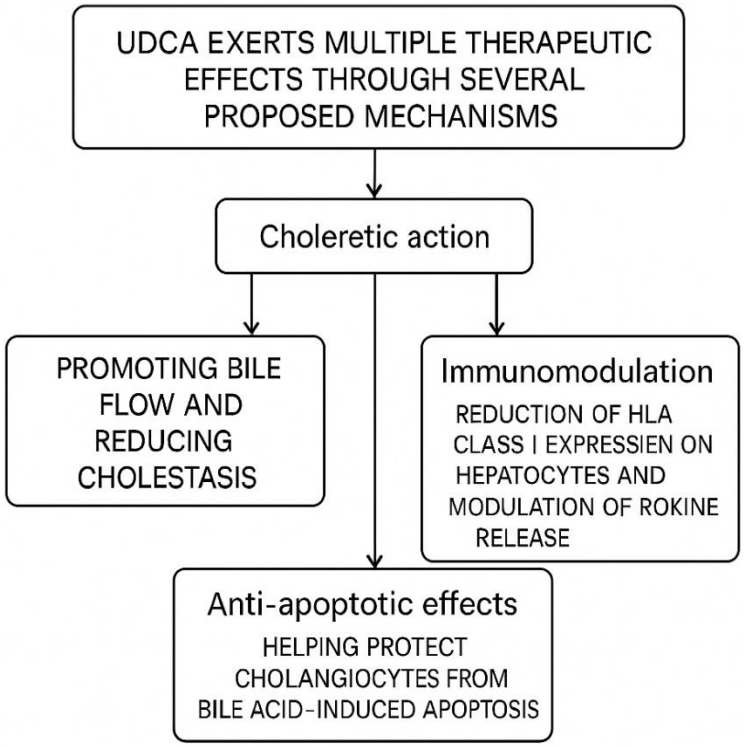

Figure 1: shows the therapeutic effect of UDCA in Primary Biliary Cholangitis (PBC).

These actions collectively improve biochemical markers of liver injury, delay histological progression, and enhance transplant-free survival [14]. Evidence from large-scale observational studies, including those by the Global PBC Study Group such as Levy et al, has validated UDCA's clinical efficacy. Compared to untreated individuals, those receiving UDCA show markedly improved outcomes, with transplant-free survival rates of approximately 90%, 78%, and 66% at 5, 10, and 15 years, respectively. In contrast, untreated patients had significantly poorer survival rates of 79%, 59%, and 32% at corresponding time points [15,16].

Regarding its safety profile, UDCA is a safe drug at the standard dose in patients with any stage of PBC, with no need for dosage adjustment in patients with other concomitant liver or renal diseases. Associated side effects include weight gain, hair thinning, mild gastrointestinal disorders such as diarrhea, nausea, and vomiting [17].

Biochemical Response Criteria:

Despite its benefits, 30–40% of patients exhibit an incomplete or inadequate biochemical response to

UDCA. These patients often show persistently elevated serum alkaline phosphatase (ALP), an indicator of ongoing cholestasis and increased risk of disease progression and elevated levels of aminotransferases and bilirubin as well [18]. Lammers et al, using a meta-analysis, on 4845 patients with PBC, stated that ALP levels above 1.5 and 3 times the upper limit of the normal range as well as abnormal serum bilirubin were the best indicators of either death or liver transplantation.10 These two indicators have now been referred to as a protocol of the surrogate biochemical endpoint of clinical trials of novel agents in PBC [19]. Several scoring systems have been developed to define response and stratify risk shown in Table 01.

Scoring System / Criteria	**Key Parameters**	**Purpose**	**Response Definition / Risk Stratification**	**Clinical Notes**
Paris I Criteria	ALP > 3× ULN, AST > 2× ULN, TB > 1 mg/dL	Biochemical response after 1 year of UDCA	Incomplete response if above thresholds	For general PBC population
Paris II Criteria	ALP or AST > 1.5× ULN, TB > 1 mg/dL	Response in early-stage PBC	Non-response if any parameter above	More sensitive in early disease
Toronto Criteria	ALP > 1.67× ULN after 12 months	Biochemical response	Incomplete response if ALP remains elevated	Simple and widely used
GLOBE Score	Age, ALP, bilirubin, albumin, platelet count (after 1 year)	Long-term prognosis	Predicts transplant-free survival	Validated internationally
UK-PBC Score	Age, ALP, bilirubin, albumin, platelet count	Prognosis in European patients	Long-term outcome prediction	Useful in routine clinical practice
Barcelona Criteria	ALP decrease ≥40% or normalization at 1 year	Biochemical response	Incomplete response if <40% decrease	Simpler but less validated
Rotterdam Criteria	Bilirubin, albumin, PT	Survival prediction	Used in advanced disease	Broader cholestatic context
Mayo Risk Score (PBC)	Age, bilirubin, albumin, PT, edema	Survival estimation	Predicts need for transplant	Developed before UDCA era

ELF Score	HA, PIIINP, TIMP-1	Fibrosis assessment	Higher scores = advanced fibrosis	Non-invasive fibrosis biomarker
Liver Stiffness Measurement (LSM)	Fibrosis stage (via elastography)	Non-invasive fibrosis monitoring	Higher kPa = worse fibrosis	Complements biochemical scores

Table 1: shows the Scoring Systems and Criteria for Evaluating Prognosis and Biochemical Response in PBC [20].

Patients failing to meet response thresholds are considered UDCA non-responders and are at significantly higher risk of adverse clinical events, including progression to cirrhosis, hepatic decompensation, and need for liver transplantation. As a result, non-responders warrant consideration for second-line or investigational therapies, prompting the exploration of additional pharmacologic agents with alternative mechanisms of action [21].

The Need for Alternative Therapeutic Strategies:

A significant challenge in the management of Primary Biliary Cholangitis (PBC) lies in the subset of patients who either fail to adequately respond to UDCA or cannot tolerate it. Inadequate biochemical response typically reflected by persistent elevation of alkaline phosphatase (ALP) and total bilirubin after one year of therapy is a strong predictor of disease progression [22]. Such patients are at increased risks of developing advanced fibrosis, cirrhosis, portal hypertension, hepatic decompensation and they might eventually need liver transplantation [23].

Reports on the effectiveness of UDCA have always been favourable but the findings of the studies conducted by Terracciani et al, indicate that 40 percent of the patients are still at risk of not responding well. This has propagated the increasing need of effective second line therapies that can not only affect biochemical surrogates but also affect clinical endpoints like symptom burden, quality of life or transplant-free survival [18,24].

Over the past few decades, there has been a growing effort to discover and evaluate novel therapeutic agents for PBC. New treatments are nuclear receptor modulators, peroxisome proliferator-activated receptor (PPAR) agonists, and additional bile acid signalling pathway regulators. This review will review these options starting with obeticholic acid (OCA) the first drug that has been approved as second line therapy and resulting to the experimental drugs which have shown good clinical results [25]. Table 02 shows an overview of therapeutic options for Primary Biliary Cholangitis (PBC).

Obeticholic Acid (OCA): The First Approved Second-Line Therapy

The semisynthetic bile acid analogue, obeticholic acid (OCA) received regulatory approvals of FDA and EMA as a second-line agent to treat the Primary Biliary Cholangitis (PBC) in patients whose condition

with disease lacks significant improvement with the ursodoxycholic acid (UDCA) treatment or with intolerability to UDCA [26]. OCA acts through selective activation of the farnesoid X receptor (FXR), a nuclear receptor that takes part in the regulation of bile acid production, liver transportation, inflammation, and fibrosis [27]. The result of FXR activation is decreasing activity of the rate-limiting enzyme in bile acid formation, the CYP7A1, and the subsequent depletion of the hepatic pool of toxic bile acids. It also enhances bile salt export pump (BSEP) and other transporter expression that causes the clearance of bile acids [28]. Moreover, OCA possesses anti-inflammatory and anti-fibrotic effects, which were proven in both preclinical and clinical trials, providing a wider hepatoprotective effect [29].

Clinical efficacy of OCA was demonstrated in the phase III POISE trial (NCT01473524), which evaluated its safety and effectiveness in patients with incomplete biochemical response to UDCA. Participants were randomized to receive either OCA 5–10 mg titration, OCA 10 mg fixed dose, or placebo, while continuing baseline UDCA therapy. After 12 months, the primary composite endpoint defined as ALP <1.67× ULN, a ≥15% reduction in ALP from baseline, and normal total bilirubin was achieved in 46–47% of OCA-treated patients compared to only 10% in the placebo group [30]. OCA also improved other liver biochemical parameters and showed reductions in markers of cholestasis and fibrosis in certain patients [31].

However, despite the clinical benefits of OCA, it is associated with notable safety concerns among which pruritus is the most common side effect, affecting over half of treated patients, and often leads to treatment discontinuation [32]. More significantly, in patients with decompensated cirrhosis or advanced hepatic impairment (Child-Pugh class B or C), OCA has been linked to worsening liver function, liver failure, and even death [33]. This prompted the FDA to issue a black box warning in 2021, restricting its use in such populations. As a result, dose adjustments or complete avoidance are recommended in patients with compromised hepatic function or concurrent liver disease [34].

In the future, various trials are going on to determine the long-term safety and therapeutic efficacy of OCA such as the COBALT trial phase IV (NCT02308111) is currently undergoing clinical-outcome measures including transplant-free survival [35]. Moreover, a combination of regimens with OCA and Biden as bezafibrate, seladelpar, or PPAR agonists is under study as a means of increasing the response and minimizing side effects [36]. Moreover, non-invasive techniques are being used more often in clinical practice of PBC patients treated with OCA: transient elastography (FibroScan) and biomarkers of fibrosis in the blood serum are becoming more often integrated in monitoring the patients and assessing the response to treatment and individual management strategies [37].

Bezafibrate: A Pan-PPAR Agonist with Strong Efficacy

Bezafibrate is a pan-peroxisome proliferator-activated receptor (PPAR) agonist that stimulates the PPAR -alpha, PPAR -delta and PPAR -gamma subtypes. This wide-range activation pattern causes bezafibrate leads to lipid, bile acid metabolism, stimulation of bile flow, anti-inflammatory, anti-fibrotic, and immunomodulatory effects [38]. Such pleiotropic effects render it an attractive drug to be used in second-line treatment of patients having Primary Biliary Cholangitis (PBC) with an insufficient response to

ursodeoxycholic acid (UDCA) [39].

The evidence in favour of the efficacy of bezafibrate has been made up of the clinical trial BEZURSO (NCT01654731), which is a phase three, double-blind, randomized, and placebo-controlled study involving 100 patients of PBC with substandard response to treatment with UDCA being subjected randomization to receive either placebo or bezafibrate (400 mg daily), and continuing with the treatment with UDCA [40]. After 24 months of treatment, 31% of patients in the bezafibrate group achieved a complete biochemical response defined as normalization of serum ALP, AST, ALT, bilirubin, albumin, and prothrombin time meanwhile compared to 0% in the placebo group [40]. Bezafibrate also conferred additional benefits, including reductions in pruritus severity, improvements in liver stiffness as assessed by elastography, and favorable changes in lipid profiles [41].

Beyond monotherapy, bezafibrate is gaining attention for its potential role in combination regimens. Preliminary data from small case series by Soret et al, indicate that triple therapy consisting of UDCA, obeticholic acid (OCA), and bezafibrate may lead to superior biochemical and symptomatic responses in some patients with difficult-to-treat PBC [42]. However, these observations remain exploratory, and larger randomized controlled trials are required to validate the efficacy and safety of such combinational strategies.

Bezafibrate is generally well tolerated; however, it is not without safety concerns. The most common adverse events include myalgia and elevations in serum creatinine, particularly among older patients or those with underlying renal impairment [43]. Rare but serious cases of rhabdomyolysis have been reported, especially when bezafibrate is co-administered with statins. Reversible elevations in liver transaminases can also occur, underscoring the importance of regular liver function monitoring. Consequently, careful patient selection and ongoing biochemical surveillance are essential components of safe and effective bezafibrate therapy in PBC [44].

Other PPAR Agonists: Fenofibrate, Saroglitazar, and Seladelpar

Fenofibrate: A Selective PPAR-α Agonist

Fenofibrate, a selective PPAR-α agonist, has been used off-label in PBC patients, particularly in Asia and Europe to enhance bile acid excretion and mitigate cholestatic injury [45]. Observational studies such as Han et al. report that adding fenofibrate to UDCA reduces serum ALP and GGT, improves liver stiffness measurements, and alleviates symptoms such as fatigue and pruritus [46]. A landmark study by Chung et al. even demonstrated improved transplant-free survival with UDCA plus fenofibrate versus UDCA alone. However, complete biochemical remission remains uncommon, long-term mortality benefit is unproven, and the potential for hepatotoxicity necessitates close monitoring of liver function tests during the first 6–12 months of therapy [47].

Saroglitazar: A Dual PPAR-α/γ Agonist

Saroglitazar is a dual PPAR-α/γ agonist approved in India for dyslipidemia and NASH that has attracted interest for PBC. Its combined modulation of lipid metabolism, anti-inflammatory action, and

enhancement of insulin sensitivity provide a theoretical rationale in cholestatic disease, and early trials suggest reductions in hepatic inflammation and fibrosis. Yet, occasional elevations in serum transaminases have been observed, underscoring the need for further studies to establish both efficacy and safety in PBC [48].

Seladelpar (MBX-8025): A Selective PPAR-δ Agonist

Seladelpar (MBX-8025) is a selective PPAR-δ agonist that exerts choleretic, anti-inflammatory, and anti-pruritic effects. Although its development was briefly paused during the ENHANCE trial over hepatotoxicity concerns in NASH patients, PBC-specific studies employing adjusted dosing and safety criteria resumed without similar adverse signals [49]. In the pivotal RESPONSE phase III trial (NCT04620733), 25% of seladelpar-treated patients achieved ALP normalization versus only 0% on placebo; total bilirubin levels fell, and pruritus scores improved significantly. Seladelpar is generally well tolerated and has received FDA Breakthrough Therapy designation for PBC [50].

Elafibranor: A Dual PPAR-α/δ Agonist

Elafibranor is a dual PPAR-α/δ agonist designed to target both bile acid metabolism and inflammatory pathways central to PBC pathogenesis. In a recent phase II study (NCT03124108), 67–79% of patients met a composite biochemical endpoint (≥15% ALP reduction, ALP <1.67× ULN, and normal bilirubin), and pruritus severity declined markedly [51]. Gastrointestinal side effects are nausea and mild abdominal discomfort were the most common adverse events and were transient. No significant hepatotoxicity emerged in PBC cohorts, and elafibranor has now earned FDA approval as a second-line therapy in this indication [52].

Farnesoid X Receptor Agonists (FXR):

Tropifexor:

Tropifexor is a potent non-bile acid farnesoid X receptor (FXR) agonist initially evaluated in animal models of cholestatic liver disease and non-alcoholic steatohepatitis (NASH). It has demonstrated the ability to reduce hepatic inflammation, steatosis, and gamma-glutamyl transferase (GGT) levels in a dose-dependent manner, accompanied by increased fibroblast growth factor-19 (FGF-19) levels [53]. In NASH trials (NCT02855164), tropifexor was associated with minimal pruritus and a stable lipid profile [54]. A separate phase II, randomized, double-blind, placebo-controlled study in PBC patients (NCT02516605) revealed a statistically significant and dose-dependent reduction in GGT levels without serious adverse events. These results are promising, although further clinical trials are necessary to validate its long-term efficacy and safety in PBC [55].

Cilofexor:

Cilofexor, another FXR agonist, has shown potential in improving cholestatic liver injury and correcting transaminase abnormalities, particularly in patients with primary sclerosing cholangitis (PSC) and NASH. However, its benefits in PBC are less clear [56]. While cilofexor monotherapy has not shown a

significant effect on hepatic fibrosis in NASH trials, it has been linked to moderate-to-severe pruritus in some patients though possibly less severe than that observed with obeticholic acid (OCA) [57]. A single NIH-funded trial investigating cilofexor in PBC (NCT02943447) was terminated early due to the emergence of alternative therapeutic options, limiting its current relevance [17].

EDP-305:

EDP-305, also an FXR agonist, has been shown to mitigate hepatic and interstitial renal fibrosis in preclinical models and early NASH studies. Despite these promising preclinical outcomes, its performance in PBC has been disappointing [58]. The INTREPID trial (NCT03394924), a phase II clinical trial in PBC patients, failed to meet its primary endpoint of achieving a 20% reduction in serum alkaline phosphatase (ALP) [59]. Although initial expectations were high, further studies are required to determine whether EDP-305 or similar agents might still have a role as disease-modifying therapies in PBC.

Mesenchymal stem cell (MSC):

Mesenchymal stem cell (MSC) therapy is a novel investigational approach that targets immune dysregulation in PBC. MSCs function by suppressing T-cell activity and modulating immune-mediated hepatic injury [60]. A phase I/II study administered MSCs at a dose of 0.5×10^6 cells/kg body weight at weeks 0, 4, and 8. ALP levels were monitored across several time points (weeks 0 to 48), and a significant reduction in serum ALP was observed at 48 weeks, dropping from a baseline average of 474.29 ± 223.26 IU/L. However, the study was limited by its small sample size [61]. A follow-up phase II trial is currently recruiting patients and will evaluate different dosing strategies ($0.1–1 \times 10^6$ cells/kg at the same 3-dose schedule). The primary endpoint in this study is the absolute change in ALP after one year of initial treatment. While results are pending, MSC therapy represents a novel immunomodulatory strategy with potential long-term benefits [61].

Investigational Agents and Emerging Therapeutics:

A new wave of therapeutic agents is being developed to target both the symptoms and underlying pathology of Primary Biliary Cholangitis (PBC), particularly for patients who have inadequate responses to existing treatments or suffer from treatment-limiting symptoms such as pruritus.

IBAT Inhibitors: Linerixibat and Maralixibat

Ileal bile acid transporter (IBAT) inhibitors such as linerixibat and maralixibat represent a novel class of drugs that alleviate pruritus by blocking the apical sodium-dependent bile acid transporter (ASBT) in the ileum, thereby reducing the enterohepatic recirculation of bile acids [62]. Linerixibat has shown a significant reduction in itch intensity in randomized phase II and III trials, without adversely affecting liver enzymes or synthetic liver function [63]. Maralixibat, already approved for Alagille syndrome, is currently under investigation in PBC, with early results suggesting meaningful pruritus relief [64]. These agents are especially beneficial for patients with refractory pruritus who do not respond to conventional treatments like bile acid sequestrants or rifampicin [62].

NOX Inhibitors: Setanaxib (GKT831):

Setanaxib (GKT831), a NOX1/NOX4 inhibitor, represents a different mechanism of action by targeting NADPH oxidase isoforms that mediate oxidative stress and fibrogenesis [65]. In a phase II clinical trial (NCT03226067), setanaxib demonstrated reductions in ALP and liver stiffness, indicating potential benefits in halting disease progression [66]. The ongoing TRANSFORM phase III trial is further evaluating its efficacy on fibrosis progression and clinical outcomes, positioning setanaxib as a promising anti-fibrotic agent in PBC [67].

Budesonide:

Budesonide, a corticosteroid with high first-pass hepatic metabolism, has been employed in PBC patients, especially those with features overlapping autoimmune hepatitis (AIH). When used alongside UDCA, budesonide can modestly improve ALP and transaminase levels; however, histological improvements are inconsistent [68]. Its long-term use is limited by the risk of portal hypertension, especially in patients with advanced disease, and the absence of survival benefit. Thus, budesonide is generally reserved for overlap syndromes rather than standard PBC management [69].

Anti-IL-31 Therapy: Nemolizumab

Nemolizumab, a monoclonal antibody targeting the interleukin-31 (IL-31) receptor A, represents an exciting development in the treatment of cholestatic pruritus. IL-31 is a pruritogenic cytokine found at elevated levels in cholestatic liver diseases, including PBC. Early-phase trials of nemolizumab have shown a significant reduction in pruritus intensity and improvement in sleep quality, making it a promising option for symptom management in patients with intractable itch [70].

FGF19 Analog: NGM282 (Aldafermin)

NGM282 (aldafermin), an engineered fibroblast growth factor 19 (FGF19) analog, functions as an FXR agonist with hepatoprotective and bile acid-lowering properties. Clinical studies have demonstrated reductions in ALP and hepatic steatosis. However, pruritus is a frequently reported side effect, and no long-term survival benefit has been confirmed. Currently, NGM282 remains in early-phase development for both PBC and non-alcoholic steatohepatitis (NASH) [71].

Drug	Mechanism of Action (MOA)	Primary Endpoint	Key Findings	Limitations / Adverse Events
Obeticholic Acid (OCA)	FXR agonist; inhibits bile acid synthesis and enhances bile acid excretion	ALP <1.67× ULN, ≥15% ALP reduction, normal bilirubin (POISE trial)	46–47% met endpoint; reduced cholestasis and fibrosis markers	Pruritus (>50%); black box warning in advanced cirrhosis

Bezafibrate	Pan-PPAR agonist (α, δ, γ); enhances bile flow and modulates inflammation	Complete biochemical response (normal ALP, AST, ALT, bilirubin, albumin, PT)	31% response vs. 0% placebo; improved liver stiffness, pruritus	Myalgia, ↑ creatinine, rare rhabdomyolysis with statins
Fenofibrate	Selective PPAR-α agonist; promotes bile acid excretion	Biochemical and symptomatic improvement	Reduced ALP, GGT, pruritus; better transplant-free survival in observational study	Less frequent full remission; hepatotoxicity risk
Saroglitazar	Dual PPAR-α/γ agonist; modulates lipids and inflammation	Reduction in transaminases, fibrosis (early trials)	Preliminary reduction in hepatic inflammation and fibrosis	Elevated liver enzymes; limited data in PBC
Seladelpar	Selective PPAR-δ agonist; anti-inflammatory and anti-pruritic	ALP normalization (RESPONSE trial)	67% met endpoint vs. 2% placebo; reduced bilirubin, improved pruritus	Initially paused due to NASH safety concerns; well-tolerated in PBC
Elafibranor	Dual PPAR-α/δ agonist; targets bile acid metabolism and inflammation	ALP <1.67× ULN, ≥15% ALP reduction, normal bilirubin	67–79% met endpoint; improved pruritus; FDA approved	Mild GI side effects; no major hepatotoxicity
Linerixibat	IBAT inhibitor; blocks bile acid reabsorption in ileum	Reduction in pruritus intensity	Significant itch reduction without worsening liver enzymes	GI upset; symptom-targeted only

Maralixibat	IBAT inhibitor	Itch relief	Early data show pruritus improvement	Emerging data; GI side effects possible
Setanaxib (GKT831)	NOX1/NOX4 inhibitor; reduces oxidative stress and fibrosis	Reduction in ALP and liver stiffness (phase II)	Positive interim results; TRANSFORM phase III ongoing	Still investigational; long-term data awaited
Budesonide	Corticosteroid with high hepatic first-pass metabolism	Modest ALP/transaminase improvement	Some benefit in PBC-AIH overlap syndromes	Risk of portal hypertension; not standard PBC therapy
Nemolizumab	Anti-IL-31Rα monoclonal antibody	Pruritus reduction	Improved itch and sleep in early trials	Symptom management only; early-phase data
NGM282 (Aldafermin)	FGF19 analog; FXR agonist; reduces bile acids and steatosis	ALP and liver fat reduction	Reduced ALP, liver fat in NASH trials	Pruritus common; no long-term survival benefit confirmed
Tropifexor	FXR agonist; induces FGF19 and reduces GGT	GGT reduction (NCT02516605)	Dose-dependent GGT reduction; minimal pruritus; no SAEs	Early-phase; further studies needed
Cilofexor	FXR agonist; improves cholestatic injury markers	N/A in PBC (trial terminated early)	Effective in PSC/NASH; moderate pruritus	NIH PBC trial terminated; moderate efficacy; limited PBC data

EDP-305	FXR agonist; reduces hepatic fibrosis (preclinical)	≥20% ALP reduction (INTREPID trial)	Failed to meet endpoint in PBC trial	No benefit in INTREPID PBC trial; requires further study
Mesenchymal Stem Cells (MSC)	T-cell immunosuppressive; immunomodulatory therapy	ALP change over 48 weeks / 1 year	Significant ALP reduction in small phase I/II study	Small sample; phase II underway; results pending

Table 2: Provides an overview of available therapeutic options for Primary Biliary Cholangitis (PBC).

Combination and Triple Therapies:

Since Primary Biliary Cholangitis (PBC) is a complicated and multi-factorial condition, the concept of multi-targeting treatment schemes is becoming more real and highly desirable. The use of a combination therapy of ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) is already strongly backed with results of improvement of serum alkaline phosphatase (ALP), bilirubin, and long-term clinical outcomes in the responders of the POISE trial [72]. UDCA in combination with fibrates, has also been used widely especially bezafibrate or fenofibrate, and has demonstrated an improved effectiveness especially in Asians and Europeans [45]. This two-combination therapy provides additive benefits when it comes to pruritus, gamma-glutamyl transferase (GGT), and measurements of liver stiffness. Nevertheless, these regimens require frequent observation of liver functions tests (LFTs) as well as renal parameters because of possible adversaries [72,45].

A new treatment on the scene is the triple therapy of UDCA, OCA, and a fibrate. The retrospective studies by Soret et al. indicate that about 60 to 70 percent of the patients on this regimen resulted in biochemical response, including substantial symptomatic relief [42]. These preliminary findings are promising but the effectiveness and safety of triple therapy needs to be confirmed using large-scale prospective trials. These combination therapies appear to have led to a convergence of thought in a recessive direction toward individualized aggressive interventions in patients who have not responded so completely to monotherapy [73].

Personalized Treatment and Risk Stratification:

Personalized medicine is the new way to go in the treatment paradigm of PBC, and risk stratification has been identified as a key determinant towards targeted therapeutics. Multiple established scoring systems support clinicians to forecast about disease progression and long-term survival [74]. GLOBE score uses age, ALP, bilirubin, albumin, and count of platelets as factors to estimate the survival of 5-, 10-, and 15-years without transplants. Likewise, UK-PBC risk score is based on overlapping variables, and it has already shown high predictive power, mainly in the European populations [75].

Further the risk is achieved by liver stiffness measurement (LSM) by transient elastography. A value of 15 kPa constitutes a high risk of hepatic decompensation, and hepatic tenders which are less than 8 kPa indicate a good long-term prognosis [76]. EASL guidelines indicate that the response to treatment should be determined twelve months after the implementation of UDCA. The patients are categorised as non-responders when their ALP levels are above the upper limit of normal (ULN) by at least 1.67, or when they have increased levels of bilirubin [77]. Such people need to be switched to second-line treatment using OCA or fibrate as soon as possible. When biochemical goals have not yet been achieved, a switch to triple therapy or inclusion in clinical trials of new drugs should be made. The strategy highlights the importance of early, customized intervention in maximising outcomes in PBC [42].

Future Perspectives and Evolving Landscape of PBC Management:

The treatment landscape for Primary Biliary Cholangitis (PBC) is evolving rapidly, offering real potential to achieve normalized liver biochemistry, symptom control, and prevention of disease progression and liver transplantation [78]. While ursodeoxycholic acid (UDCA) continues to serve as the first-line therapy, advances in risk stratification tools such as the GLOBE and UK-PBC scores, along with non-invasive assessments like transient elastography, allow for early identification of incomplete responders who may benefit from second-line agents [79]. The growing armamentarium of therapies including FXR agonists, PPAR modulators, NOX inhibitors, and novel immunomodulatory strategies demonstrates a shift toward mechanism-based, patient-specific treatment plans. Promising investigational therapies like norucholic acid and stem cell-based interventions, alongside immune tolerance induction targeting PDC-E2, reflect the innovative directions being explored [80]. The increased attention to other important aspects, such as the enhancement of quality of life due to quality symptom control, i.e., pruritus and fatigue, much attention is also attracting numerous agents in development or in advanced trials. With the trend towards early intervention and combination treatment regarding clinical paradigm use, the future of treatment in PBC promises not only the biochemical remission but also an increased well-being of patients [81].

CONCLUSION

In conclusion, Primary Biliary Cholangitis is no longer a condition that has presented few therapeutic options but rather one that has remained in the forefront of innovation in hepatology. Although UDCA still forms the basis of treatment, the arrival of second-line drugs of high strength and the advancing knowledge in the fields of disease pathology has helped construct more customized, successful, and reasoned modes of therapy. It seems we are on the cusp of a new phase in PBC management, however, which judges not only by its extended longevity but also the day-to -day quality of life of individuals with this chronic disease.

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