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Quality of Life in Primary Biliary Cholangitis- Advances in the Treatment

Jakość Życia w Pierwotnym Zapaleniu Dróg Żółciowych – Postępy w Leczeniu

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Abstrakt

Pierwotne stwardniające zapalenie dróg żółciowych (PSC) to zapalna, cholestatyczna i postępująca włókniejąca choroba wątroby pozbawiona skutecznej interwencji medycznej. PBC to przypuszczalnie immunologiczna choroba wątroby u kobiet w średnim wieku, związana ze znaczną zachorowalnością i śmiertelnością. Osoby żyjące z PBC często mają objawy, odczuwają obciążenie jakością życia, na które składają się zmęczenie, świąd, ból brzucha i zespół suchości. Przebadano wiele leków pod kątem leczenia, w tym środki o właściwościach żółciopędnych i immunosupresyjnych. Przyszła licencjonowana terapia PBC prawdopodobnie będzie obejmować agonistów szlaku receptora aktywowanego przez proliferator peroksysomów (PPAR), w tym specyficzny agonizm PPAR-delta (seladelpar), a także elafibrynor i saroglitazar (oba z szerszym agonizmem PPAR). Skuteczna terapia zmniejsza potrzebę przeszczepu i poprawia oczekiwaną długość życia.

Abstract

Primary sclerosing cholangitis (PSC) is an inflammatory, cholestatic and progressively fibrotic liver disease devoid of effective medical intervention. PBC is a presumed immune-mediated liver disease of middle-aged women associated with significant morbidity and mortality. People living with PBC are frequently symptomatic, experiencing a quality-of-life burden dominated by fatigue, itch, abdominal pain, and sicca complex. Many drugs have been studied for treatment, including agents with choleretic and immunosuppressive properties. Future PBC licensed therapy will likely include peroxisome proliferator activated receptor (PPAR) pathway agonists, including specific PPAR-delta agonism (seladelpar), as well as elafibrinor and saroglitazar (both with broader PPAR agonism). Effective therapy reduces the need for transplantation and improves life expectancy.

Keywords: primary biliary cholangitis, treatment, ursodeoxycholic acid, quality-of-life, cholestasis, inflammatory, activity

Introduction

Primary biliary cholangitis (PBC) is a chronic, autoimmune, cholestatic liver disease characterized by inflammation and destruction of intrahepatic bile ducts by the immune system, leading to cholestasis, fibrosis and cirrhosis of the liver [1,2,3]. If left untreated, PBC can result in liver failure and death [4]. The disease is rare, with an incidence of 30-40 cases per 100,000 people, predominantly affecting women at a ratio of 9:1, likely due to genetic and epigenetic factors [1,3]. The highest incidence occurs in the fourth and fifth decades of life. The pathogenesis of PBC is still not fully understood, so treatment mainly focuses on alleviating symptoms, preventing avoidable complications and slowing disease progression [5]. The clinical presentation of PBC varies and depends largely on the stage of the disease at diagnosis. It includes mostly asymptomatic cases but can also present with severe symptoms such as pruritus, fatigue, upper right quadrant abdominal pain, sicca syndrome and jaundice, significantly impacting the quality of life [6,7]. Early-onset cholestasis usually indicates a late diagnosis at the cirrhosis stage or severe early bile duct loss [1]. Laboratory findings in PBC typically show cholestasis markers: elevated alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), aminotransferases and total bilirubin levels, correlating with treatment response, disease stage, and activity. Elevated serum immunoglobulin M and highly specific

antimitochondrial antibodies (AMA) or less commonly, antinuclear antibodies against glycoprotein 210 (anti-GP210) and/or sp100 (anti-SP100) are also frequently present. If AMA is absent, these two antibodies can be used for diagnosis [6,7]. PBC diagnosis is established when at least 2 out of 3 criteria are met: (1) elevated ALP, (2) presence of AMA or other disease-specific antibodies (anti-GP210 or anti-SP100) in the absence of AMA, (3) typical histological features of non-suppurative cholangitis and destruction of interlobular bile ducts on liver biopsy [8]. At diagnosis, a significant number of patients are asymptomatic. Unfortunately, up to 40% of patients develop cirrhosis within 10 years of diagnosis. In end-stage disease, complications such as liver failure or hepatocellular carcinoma may arise, leading to premature death without timely liver transplantation. The primary goals of pharmacotherapy are to slow disease progression, prolong life and alleviate symptoms [7, 9].
The aim of this article is to review the literature on medications used in the treatment of primary biliary cholangitis, with a particular focus on new pharmacological agents. Relevant studies were identified using the PubMed/MEDLINE electronic database. The search targeted publications presenting the most up-to-date knowledge in this field.

Treatment of Primary Biliary Cholangitis

Pharmacological Methods

First-line therapy for PBC is ursodeoxycholic acid (UDCA), a hydrophilic bile acid that positively impacts the course of the disease and clinical outcomes. It is administered at a therapeutic dose of 13-15 mg/kg/day. It is a safe medication that can also be given to pregnant women. It has been proven that a reduction in ALP levels due to this drug correlates with a delay in the progression to end-stage liver failure and death. The effectiveness of the treatment is evaluated after 12 months of use. Unfortunately, 15-40% of patients experience drug intolerance or an insufficient response to its action, necessitating second-line therapy in combination with UDCA [3,5,8,10]. An alternative drug is obeticholic acid (OCA), a selective agonist of the farnesoid X nuclear receptor (FXR), which can be used as an adjunct in cases of incomplete UDCA efficacy. It exhibits choleretic, anti-inflammatory and antifibrotic effects [3,7]. A year-long study demonstrated that this drug positively affects ALP levels; however, it

may exacerbate pruritus in some patients. Another drug is bezafibrate, a peroxisome proliferator-activated receptor (PPAR) agonist, used off-label [3,6]. It acts on all PPAR isoforms, hence it is called a pan-PPAR agonist [11]. PPAR activation leads to beneficial changes in bile acid metabolism: inhibition of their synthesis, increased secretion, and reduced toxicity. A two-year study showed that bezafibrate not only normalized liver parameters in many individuals but also reduced the severity of pruritus. It is another agent that can be used as an adjunct in patients with an incomplete response to UDCA, usually at a dose of 400 mg/day [1,3]. Sometimes fenofibrate, a PPAR α agonist, is also used off-label instead of bezafibrate [7,11]. Experimental studies have administered OCA and bezafibrate simultaneously, suggesting that such an approach may improve patient survival without the need for liver transplantation [10]. The high efficacy and safety of PPAR agonists have led to further research on other agonists of these receptors [3], including elafibranor, a PPAR α and δ agonist, seladelpar, a PPAR δ agonist, and saroglitazar, a PPAR α and γ agonist [2,7,11]. Another drug sometimes used in the treatment of PBC without liver cirrhosis but with significant liver inflammation is budesonide, initially usually administered at a dose of 6-9 mg/day. Clinical studies have shown that it positively affects ALP reduction. Combined treatment with budesonide and UDCA has also been shown to protect the biliary epithelium from the harmful effects of bile acids. Due to typical side effects characteristic of glucocorticosteroids, including hypertension, osteopenia, cataracts and weight gain, budesonide is unsuitable for long-term therapy. Additionally, it is not recommended for patients with liver cirrhosis due to the risk of portal vein thrombosis. All of these factors make its use rare in clinical practice [1,5,7].

Treatment of Pruritus

Pruritus occurs in 20-70% of patients with PBC, leading to sleep disturbances, fatigue, depression, social isolation and significantly reduced quality of life. Some medications used in treating the disease, such as UDCA or OCA, may exacerbate pruritus and treatment options remain limited [4,7].

For chronic cholestatic pruritus of mild intensity, the first-line treatment is cholestyramine, which can also be used in cases of poor tolerance to bezafibrate and rifampicin by patients or the presence of contraindications to their use. It is administered at a dose of 4-16 g/day before

meals and other medications or several hours after them due to its negative impact on their intestinal absorption [1,7]. In cases of moderate to severe pruritus, bezafibrate, if available, can be used as a first-line treatment at a dose of 400 mg/day. This agent reduces pruritus and favorably affects ALP levels. During therapy, it is crucial to monitor liver parameters, creatine kinase and creatinine [1,12]. An alternative medication to bezafibrate could be rifampicin, administered at a dose of 150-300 mg twice daily. Liver parameters should be monitored during treatment due to the potential toxic effect of the drug on the liver. If there is no improvement after cholestyramine, bezafibrate or rifampicin or if side effects occur, the inclusion of naltrexone (up to 50 mg/day) – an opioid antagonist and sertraline (75-100 mg/day) – a selective serotonin reuptake inhibitor, can be considered. Off-label, other medications such as bile acid-binding resins or antihistamines are also used. If the previously mentioned measures do not produce the desired effect, the next step is to refer the patient to a specialized center for experimental treatment methods [1,7].

Studies on elafibranor – a PPAR receptor agonist, have shown that this drug does not exacerbate pruritus and has shown a beneficial trend in improving pruritus and quality of life in some patients taking this agent. These preliminary assumptions, however, need to be confirmed in further studies involving a larger number of patients and over a longer duration [3,5]. Research is also ongoing on intestinal bile acid transporter (IBAT) inhibitors, such as linerixibat and volixibat, other PPAR agonists, as well as difelikefalin – a peripherally acting opioid receptor agonist [1,12]. These may potentially be used in the future.

Treatment of Chronic Fatigue

Fatigue affects many patients with PBC regardless of the stage of the disease, significantly impairing their quality of life. Unfortunately, there are still no effective pharmacological treatments available and patients are mainly advised on coping strategies and encouraged to avoid social isolation. It is also important to conduct additional tests to exclude other potential causes of fatigue that can be effectively treated, such as anemia, hypothyroidism, obstructive sleep apnea, depression or diabetes [1,6,12]. Fibrates have been shown to potentially reduce

fatigue; however, they are not routinely used due to their possible toxic effects on the liver and kidneys. Modafinil has been administered off-label in uncontrolled studies, but a randomized study did not demonstrate benefits from its use. PPAR agonists are currently being investigated [7,12].

Elafibranor

Elafibranor is a selective agonist of PPAR α and δ, an oral fibrate that has been tested for the treatment of patients with PBC who are unresponsive to or intolerant of UDCA therapy [1,3,12]. This group of patients is particularly at risk for disease progression and severe complications. Activation of PPAR receptors leads to changes in bile acid metabolism, including enhanced bile acid conjugation and secretion, as well as promoting the formation of non-toxic bile acid micelles in the bile ducts. Additionally, simultaneous stimulation of α and δ receptors exhibits anti-inflammatory effects. A randomized clinical trial of elafibranor demonstrated a reduction in ALP levels, total bilirubin, and gamma-glutamyltransferase (GGT) levels [1,2,3,5]. It was also shown that the drug caused a decrease in high-sensitivity C-reactive protein (hs-CRP) and other disease markers, and in patients with pruritus, it alleviated discomfort, leading to improvement in this regard [3,5]. During the study, patients treated with elafibranor experienced a reduction in total cholesterol, LDL cholesterol, and triglycerides, while HDL cholesterol remained stable. Reported adverse effects ranged from mild to moderate and primarily involved gastrointestinal symptoms—such as abdominal pain, nausea, vomiting, diarrhea—as well as headache and fatigue [2,3,5,7,8]. During therapy, patients receiving a high dose of elafibranor experienced a reversible and relatively significant increase in serum creatinine levels; however, the level of circulating cystatin C, an accurate marker of glomerular filtration, remained unchanged [3,5]. In mid-2024, the U.S. Food and Drug Administration (FDA) granted accelerated approval for the use of elafibranor at a dose of 80 mg orally once daily in patients with PBC, in combination with UDCA for those who do not respond adequately to UDCA therapy, or as monotherapy in patients who are intolerant to UDCA. A decision regarding the drug's authorization by the European Medicines Agency (EMA) and the UK Medicines and Healthcare Products Regulatory Agency (MHRA) is expected in the second half of 2024 [13,14].

Seladelpar

Seladelpar is a highly selective and potent PPAR-δ agonist with antiinflammatory and anti cholestatic properties. Expressed in hepatocytes, Kupffer cells, and hepatic stellate cells, PPAR-delta activation is associated with reduced bile acid synthesis, suppression of inflammatory cytokines, and inhibition of hepatic stellate cell proliferation and activation, among other important metabolic effects. Seladelpar is rapidly (Tmax approximately 1.5 hr) and almost completely absorbed after oral administration, with similar exposures (Cmax, AUC) at 5 mg in PBC patients with and with-out cirrhosis and with no accumulation following 12 weeks of exposure. It undergoes extensive oxidative metabolism and its metabolites are primarily excreted in the urine [15,16].

Despite seladelpar having a somewhat stormy start due to safety concerns around liver toxicity, these have largely been addressed by dose adjustment in PBC and an independent review into liver histology from the NASH studies. The evi-dence so far suggests that seladelpar leads to markedimprovement in liver biochemistry, positioning it as a potential alternative second-line therapy for those where OCA is not suitable, not tolerated, or ineffective. The safetydata for seladelpar are encouraging, it appears to be welltolerated, although, as with other fibrates, it is likely to requireregular monitoring to exclude renal toxicity. The data suggests that in those with compensated cirrhosis, it is well tolerated,without the need for dose adjustment, and this is an area that warrants further attention.Symptomatic PBC in particular, fatigue, remains a significant unmet need, with no effective therapies. The data on fatigue are limited, but if a beneficial effect on fatigue is confirmed, this could be a key factor for the utility of seladelpar in clinical practice given the lack of any other effective therapy. The emerging evidence that seladelpar improves pruritus is promising but should be interpreted with caution, given much of the data comes from an open-label trial, where there is likely to be a significant placebo effect. Future trials will likely provide a clearer picture to the effectiveness of seldelpar on symptomatic PBC. How seldelpar equates to other fibrates and FXR agonists remains to be seen, with no planned head-to-head trials to compare against it is likely to be at least comparable to other fibrates in terms of efficacy and tolerability but will perhaps have the advantage of having more robust underpinning evidence and, in due course, data, to demonstrate its effect on hard outcomes in PBC [17].

PBC patients treated with seladelpar for 1 year displayed improvements in pruritus, sleep disturbance and fatigue compared with baseline. Improvement in pruritus was associated with the changes in total bile acids and certain bile acid subspecies.

Saroglitazar, Norursodeoxycholic acid (norUDCA), NOX inhibitors, Nudt1, FGF 19, JAK inhibitors

Saroglitazar is a novel dual-PPAR (alpha-gamma) agonist. It is indicated for the treatment of diabetic dyslipidemia and hypertriglyceridemia with type 2 diabetes mellitus not controlled by statin therapy [18]. In clinical studies, saroglitazar has demonstrated reduction of triglycerides (TG), LDL cholesterol, VLDL cholesterol, non-HDL cholesterol and an increase in HDL cholesterol a characteristic hallmark of atherogenic diabetic dyslipidemia (ADD). Due to similarities in the mechanistic pathogenesis, the efficacy of saroglitazar is being evaluated in the management of PBC as a second-line therapy [19].

Norursodeoxycholic acid (norUDCA) is the C23 (C24-nor) homolog of UDCA. UDCA (3α,7β-dihydroxy-5β-cholanoic acid) is normally present in human bile, amounting to 1–3% of biliary BA [20]. In healthy human volunteers, norUDCA ingestion induces hypercholeresis and evokes less phospholipid and cholesterol secretion into bile than UDCA. It has shown potent anti-cholestatic, anti-inflammatory and anti-fibrotic properties [4]. It is also distinguished by its intrahepatic enrichment, leading to a possible role in non-cholestatic metabolic and inflammatory liver disease [4].

The NOX enzymes catalyse the NADPH-dependent reduction of oxygen to form superoxide, which can react with itself to form hydrogen peroxide (H2O2). Accumulating evidence has suggested a critical role of NADPH oxidase (NOX), a multi-component complex that catalyzes reactions from molecular oxygen to reactive oxygen species (ROS), in the activation process of hepatic myofibroblasts. NOX isoforms, including NOX1, NOX2 and NOX4, and NOX-derived ROS, have all been implicated to regulate hepatic stellate cells activation and hepatocyte apoptosis, both of which are essential steps for initiating liver fibrosis. NOX4 additionally promotes the signaling of transforming growth factor beta (TGFb-1), which contributes to fibrinogenesis in PBC [21]. This suggests that selective NDAPH oxidase inhibitors, such as NOX4 inhibitors, might be a promising therapeutic agent.

NUDT1 (Nudix Hydrolase 1) is a protein coding gene. Misincorporation of oxidized nucleoside triphosphates into DNA/RNA during replication and transcription can cause mutations that may result in carcinogenesis or neurodegeneration. Nudt1 mediates the inappropriate expansion,

hyperactivation, and long-term survival of CD 103+ cells, the primary autoreactive T cells demonstrating cytotoxicity against cholangiocytes in patients with PBC. The data suggests that future immune-based therapies of relapsed/refractory PBC could focus on the elimination of CD103+ TRM cells [22].

Fibroblast growth factor 19 (FGF19), an endocrine gastrointestinal hormone, controls bile acid metabolism via actions on CYP7A1, the first and rate-limiting enzyme in the classic pathway of bile acid synthesis. FGF-19 agonists have been shown to have anti-steatotic, anti-inflammatory, and anti-fibrotic properties [23].

Barcitinib, a JAK 1 and JAK 2 inhibitor, is hypothesized to downregulate multiple cytokines involved in PBC pathogenesis. Further studies are needed to evaluate the efficacy and safety [24].

Transplantation

Transplant is not a panacea for patients (there are challenges around access, especially for women with PBC and patients in minority groups, poor organ quality with long-term sequelae, and, crucially, quality of life after transplant) and it is reasonable to aspire to avoid it if at all possible. This change has come about through a combination of better awareness among patients and clinicians, increasing access to diagnostic tests, and, most notably, through the advent of effective treatment regimens and early prescription [25].

Conclusion

Primary biliary cholangitis is a rare inflammatory condition of the bile ducts. PBC is a presumed immune-mediated liver disease of middle-aged women associated with significant morbidity and mortality. To date, there is a wide spectrum of therapeutic options for PCB. According to guidelines, UDCA is the first line of treatment in patients with PBC followed by OCA. Patients who have suspected PBC undergo evaluation to establish the diagnosis early and UDCA therapy should be initiated promptly as treatment with UDCA may delay disease progression and prolong survival free of liver transplantation. Despite the presumed autoimmune etiology of PBC, a clear benefit from immunosuppressive agents has not been demonstrated to date and their use can be limited by side effects. Further studies are needed for development of an optimal therapeutic strategy for patients who have PBC to cure or halt progression of disease, thereby decreasing incidence of complications of advanced liver disease and the need for transplantation and extending life expectancy in all patients who have PBC.

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