Review

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Iqirvo for primary biliary cholangitis – efficacy, safety, and future directions

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Abstract

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by progressive bile duct destruction, leading to cirrhosis and liver failure. Recent advancements in treatment have focused on targeting specific molecular pathways involved in the disease's pathogenesis. Iqirvo, a dual peroxisome proliferator-activated receptor alpha and delta agonist, has shown promise in addressing the unmet medical needs of PBC patients. This review examines the clinical development and efficacy of Iqirvo, which recently received accelerated approval from the U.S. Food and Drug Administration. The approval was based on data demonstrating improvements in biochemical markers associated with liver function and bile acid metabolism. We also discuss the safety profile, potential side effects, and future implications for the management of PBC. The expedited approval of Iqirvo represents a significant advancement in PBC therapy, offering new hope for patients unresponsive to existing treatments.

Keywords: autoimmune disease, biliary, liver cirrhosis, peroxisome proliferator-activated receptor alpha, primary biliary cholangitis, united states food and drug administration

Introduction

Primary biliary cholangitis (PBC) is a chronic, inflammatory, autoimmune, cholestatic liver disease which is strikingly more prevalent in females[1]. It is manifested by the interlobular bile ducts being destroyed by T-Cell lymphocytes, which causes cholestasis to worsen and results in jaundice, pruritus, and hypercholesterinemia. This can lead to biliary cirrhosis or hepatocellular carcinoma, which may require a liver transplant or even cause death[2]

PBC, being more common in women than in men, has a female-to-male ratio closer to 4–6:1, like other autoimmune illnesses. Nonetheless, the overall mortality rate for male patients is considerably greater[3]

Worldwide, incidence and prevalence of PBC were 1.76 and 14.60 per 100 000 individuals respectively. It varied widely across regions, with North America (2.75%) being the highest, followed by Europe (1.86%), and the lowest in the Asia-Pacific region (0.84%)[4]. Nevertheless, recent data indicates that in the Asia-Pacific region, the prevalence and incidence of PBC are higher (11.9%) than once expected as PBC tends to be diagnosed at older age and has a relatively low incidence of HCC in this region[5]

Age-related trends in its incidence and prevalence are seen, with a peak range of 60–79 years old. PBC is predominantly seen in middle-aged people (40-60 years old), and it appears to be rare in those under 25 years of age[6]

HIGHLIGHTS

- Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease that affects bile ducts, causing cholestasis, jaundice, and potential liver damage, leading to cirrhosis or hepatocellular carcinoma.
- Iqirvo, a PPAR agonist, that helps reduce bile acid production and improves lipid profile, was approved by the FDA in June 2024 for PBC patients not responding to ursodeoxycholic acid or intolerant to it.
- Current treatment options for primary biliary cholangitis includes ursodeoxycholic acid, obeticholic acid, fibrates, such as bezafibrate and liver transplant.
- In the ELATIVE trial, the drug showed a significant reduction in alkaline phosphatase levels, demonstrating overall efficient clinical activity. It is well-tolerated with manageable side effects.
- More studies about the efficacy and safety of the drug are necessary to confirm the side effects of prolonged treatment and its limitations.

Pathophysiology

PBC is a multifactorial disease; it remains unknown how and why PBC develops but genetic predisposition is believed to be a major contributing factor in its development[7] Tolerance

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breakdown triggers disease onset and the attack is targeted at biliary epithelial cells. The hallmark of PBC is anti-mitochondrial antibody (AMA), which are detected in 90–95% of patients with PBC[8] Furthermore, and independent of AMA status, 30% of patients may develop different PBC-specific antinuclear autoantibodies such as anti-gp210 and anti-p62 (with 95% specificity for PBC each) as well as anti-sp100, anti-PML and anti-sp140[9]

The unique pathological picture in PBC is the presence of dense portal and periportal inflammatory infiltrates comprising of $CD4^+$ and $CD8^+$ T cells, macrophages, eosinophils, B lymphocytes, plasma cells, NK and NKT cells, which surround the small and medium-sized intrahepatic bile ducts. These inflammatory cells disrupt the biliary lumen by permeating the biliary epithelium[10]

PBC patients often exhibit a wide range of symptoms at first. Fatigue and pruritus are the most common clinical symptoms in the early stages of PBC, followed by jaundice. Fatigue, being the most common and debilitating symptom in PBC, is experienced by approximately 50% of patients. Pruritus, another common symptom in PBC, affects 20–80% of patients[11]Patients with chronic cholestasis are at risk for developing osteopenia and osteoporosis[12], hyperlipidemia, metabolic syndrome, fat-soluble vitamin deficiencies[13] and sicca complex syndrome (dry eyes and dry mouth). These escalating symptoms lower quality of life and increase the risk of depression and social isolation[14].

Current treatments for primary biliary cholangitis

First line therapy

Ursodeoxycholic acid (UDCA)

All PBC patients with elevated liver biochemistry levels are recommended to take UDCA, which has been approved as a first-line treatment for PBC globally, at a dose of 13–15 mg/kg/day[15-17]. Utilizing several intricate and complementary methods, ursodeoxycholic acid affects the liver by acting as a choleretic, immunomodulator, cytoprotectant, and changing the bile acid pool. By blocking the absorption of cholesterol in the intestine and its release into bile, it significantly reduces biliary cholesterol saturation[18] UDCA is a well-tolerated drug. AEs include diarrhea, upper right quadrant abdominal pain, skin reactions and worsening pruritis[19] Some patients develop hair thinning and gain weight[20] It is contraindicated in patients with obstructive cholestasis[21] in the first trimester of pregnancy.

Second line therapy

Obeticholic acid (OCA)

When UDCA fails to provide sufficient relief, OCA is recommended as an adjuvant therapy[22]. For patients who are intolerant to UDCA, OCA can likewise be given as monotherapy[23]. Obeticholic acid is a modified, synthetic bile acid that functions as a farnesoid X-activated receptor (FXR) agonist. FXRs mediate the production of bile acids and release fibroblast growth factor, specifically FGF-19, into the hepatic portal circulation. By decreasing the hepatic exposure to bile acids, the progression of PBC is limited[24,25]. The most frequent adverse effects include dose dependent pruritus, fatigue, and abdominal pain/discomfort. Additional side effects that have been observed include include rash, oropharyngeal pain, dizziness, constipation, arthralgia, dyslipidemia, headache, eczema, depression, hypersensitivity reactions, and altered thyroid function[26]. In a 3-year interim analysis of patients in the POISE trial, hepatic adverse events such as esophageal varices and ascites also occured[27]. In addition, FXR activation by OCA causes a negative impact on the lipid panel as it decreases HDL and increases LDL-cholesterol, independently of the dose[28]. Obeticholic acid is contraindicated in patients with complete biliary obstruction.

Fibrates

Fibrates are used off-label in PBC as its use has improved outcomes for patients[29]Bezafibrate, a dual PPARs/PXR agonist showed to have potent anticholestatic efficacy in early-stage PBC patients with an incomplete biochemical response to UDCA monotherapy[30]. Fibrates are peroxisome proliferator-activated receptor (PPAR) agonist. They also cause an overall decrease in very-low-density lipoproteins and decrease the availability of substrate for triglyceride synthesis in the liver; they also increase the activity of lipoprotein lipase; modulate the interaction between the LDL receptor and ligand; and stimulate reverse cholesterol transport[31]. Fibrates are considered safe and well tolerated in patients with PBC, with a low frequency of AEs. Most common experienced side effects were musculoskeletal pain, gastrointestinal disturbances, and mild elevation of ALT, AST and creatinine[32]Liver and renal function should be monitored periodically in PBC patients on fibrates, and its use should be avoided in those with decompensated liver disease.

Liver transplant

For individuals experiencing decompensating episodes or unbearable pruritus, liver transplant remains the only therapy choice despite advancements in medical treatment[33] recurrence is common.

Advent and approval of IQIRVO

After a series of clinical testing and trails conducted, the medication Iqirvo was given an accelerated approval for the treatment of PBC in combination with UDCA in patients presenting an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA by U.S. Food and Drug Administration (FDA) in June 2024. This approval was granted significantly based on the trial data from the Phase III ELATIVE, a multicenter, randomized double-blind, placebo-controlled Phase III clinical trial (n = 161)[34]

The administration of Iqirvo did not elevate the risk of serious adverse events or events leading to treatment discontinuation. The safety profile of Iqirvo exhibited increased survival outcomes and a remarkable reduction in the levels of alkaline phosphatase (ALP) in the patients. Thus, this compelling evidence strongly supports the approval of Iqirvo by the FDA as promising and well-tolerated therapeutic approach in the management of PBC.

Mechanism of action of IQIRVO

Iqirvo is a first-in-class oral, once-daily PPAR agonist, which works by activating PPAR-alpha and PPAR-delta receptors responsible for regulating energy homeostasis and metabolic

function[35]. PBC is a rare, autoimmune cholestatic liver disease characterized by excessive build-up of bile, toxins and inflammation leading to scarring of liver and destruction of bile ducts. The exact mechanism by which Iqirvo exerts its therapeutic effects in patients with PBC is not well understood. However, the potentially relevant affects it produces is by activating the PPAR receptors, thereby inhibiting the production of bile acids from lipids[36]. Oral administration of Iqirvo produces significant decrease in lipid profiles (fasting plasma triglycerides, γ glutamyl transferase, and LDL-cholesterol, while HDL-cholesterol) and liver enzymes owing to its efficacy and usage[37]. Thus, by inhibiting the synthesis of bile acids it exerts it effects in the patients with PBC.

Clinical efficacy of IQIRVO

The effectiveness of Iqirvo was assessed in the ELATIVE study, a Phase III clinical trial that was multi-center, randomized, double-blind, and placebo controlled. This trial included 161 adults with PBC who had an inadequate response or intolerance to UDCA. Participants, with a mean age of 57 years, were randomized to receive either 80 mg of Iqirvo daily plus UDCA (n = 108) or a placebo plus UDCA (n = 53). About 95% of patients received Iqirvo or placebo in combination with UDCA, while 5% were given Iqirvo as monotherapy due to UDCA intolerance[38,39].

The primary endpoint was a biochemical response at week 52, defined by an ALP level less than 1.67 times the upper limit of normal, a reduction of at least 15% from baseline, and normal total bilirubin levels. Secondary endpoints included the normalization of ALP levels at week 52 and changes in pruritus intensity from baseline through weeks 24 and 52, measured by the Worst Itch Numeric Rating Scale (WI-NRS)[38].

The ELATIVE trial showed that Iqirvo provided a significant treatment benefit, with 51% of patients achieving a biochemical response compared to 4% in the placebo group, resulting in a 47% treatment difference (95% CI 32, 57; $P < 0.0001$). Additionally, 15% of patients treated with Iqirvo achieved ALP normalization at week 52, compared to 0% in the placebo group ($P = 0.002$; 95% CI 6,23). Importantly, reductions in ALP levels were not only sustained through week 52 but were also evident as early as week 4 in the Iqirvo group, providing reassurance about the drug's long-term efficacy[38,39] (Table 1).

Among patients with moderate-to-severe pruritus (44 in the Iqirvo group and 22 in the placebo group), the least-squares mean change from baseline on the WI-NRS did not significantly differ between the groups (–1.93 vs. –1.15; difference, –0.78; 95% CI, –1.99 to 0.42; $P = 0.20$). The study's results indicate that Iqirvo is an effective treatment for PBC, offering significant benefits and instilling optimism about its potential impact on PBC treatment[38].

Safety and tolerance of IQIRVO

In a clinical trial involving 161 patients, the safety and tolerability of Iqirvo were thoroughly evaluated. Patients were randomized to receive either Iqirvo 80 mg (n = 108) or a placebo (n = 53) once daily, with a median exposure duration of 62 weeks during the double-blind period. The most common adverse reactions reported with Iqirvo (occurring in ≥5% of patients and more frequently than with placebo) included weight gain, diarrhea, abdominal pain, nausea, vomiting, arthralgia, constipation, muscle injury, fractures, gastroesophageal reflux disease, dry mouth, weight loss, and rash. These findings have important implications for the use of Iqirvo in the treatment of PBC[36].

It's important to note that Iqirvo's safety profile includes a Boxed Warning that highlights potential risks such as myalgia, myopathy, rhabdomyolysis, fractures, fetal harm, drug-induced liver injury, hypersensitivity reactions, and biliary obstruction. This information is crucial for healthcare professionals and patients to be fully informed and aware when considering this therapy for PBC[36].

Future applications and limitations

Iqirvo marks a notable advancement in the treatment landscape of PBC, offering a new therapeutic option for patients with limited alternatives. Its dual PPARα/δ agonist mechanism has shown promise in improving biochemical markers such as alkaline phosphatase and total bilirubin, which are crucial indicators of liver function and disease progression. Furthermore, Iqirvo's pharmacokinetic profile indicates a steady-state achievement within two weeks of daily dosing, with no significant QTc interval prolongation even at higher doses, underscoring its safety. Despite its potent activation of PPAR-alpha, Iqirvo does not elicit the adverse effects typically associated with PPAR-gamma activation, highlighting its favorable safety profile. Additionally, the metabolism and excretion pathways suggest efficient processing and elimination of the drug, with the majority being excreted via feces, minimizing potential toxicity[36]. The FDA's accelerated approval of Iqirvo is a testament to its potential benefits; however, several limitations warrant further investigation.

Firstly, the long-term effects of Iqirvo on overall survival and prevention of liver-related complications in PBC patients remain unclear. The phase 3 ELATIVE trial demonstrated significant improvements in alkaline phosphatase levels, but data on long-term outcomes are limited[38]

Additionally, the effectiveness and safety of Iqirvo in diverse patient populations, including those with advanced liver disease, comorbid conditions, or varying genetic backgrounds, are not fully understood. Specific subgroups may exhibit different responses to the therapy, necessitating tailored treatment approaches[39]. Although Iqirvo has a generally manageable safety profile, common adverse effects such as gastrointestinal disturbances, pruritus, and potential liver enzyme elevations require careful monitoring. The risk-benefit ratio in patients with pre-existing gastrointestinal or hepatic conditions needs further clarification[39]

Moreover, the potential for Iqirvo to be used in combination with other therapies for PBC, such as obeticholic acid or ursodeoxycholic acid, is an area of interest that requires further research. Combination therapies could potentially enhance therapeutic outcomes, but the safety and efficacy of such combinations are not yet established[38]

The continued approval and market acceptance of Iqirvo will depend on demonstrating sustained clinical benefits and a favorable safety profile in real-world settings. The regulatory landscape and healthcare policies could impact the accessibility and adoption of the therapy[39]

Table 1

Summary of the clinical trial.

Study ID	Drug	Phase	Sample size	Outcomes	Adverse effect
ELATIVE trial (NCT04526665)[38]	In the 52-week, double-blind, placebo-controlled trial, patients were randomly assigned (in a 2:1 ratio) with primary biliary cholangitis who had had an inadequate response to or unacceptable side effects with ursodeoxycholic acid to receive once-daily Iqirvo, at a dose of 80 mg, or placebo.	Phase 3	161 adults with primary biliary cholangitis (PBC) who had an inadequate response or intolerance to ursodeoxycholic acid (UDCA), with a mean age of 57 years.	The primary endpoint was a biochemical response at week 52, defined by an alkaline phosphatase (ALP) level less than 1.67 times the upper limit of normal, a reduction of at least 15% from baseline, and normal total bilirubin levels. Secondary endpoints included the normalization of ALP levels at week 52 and changes in pruritus intensity from baseline through weeks 24 and 52, measured by the Worst Itch Numeric Rating Scale (WI-NRS)	The most common adverse reactions reported with IQIRVO (occurring in ≥ 5% of patients and more frequently than with placebo) included weight gain, diarrhea, abdominal pain, nausea, vomiting, arthralgia, constipation, muscle injury, fractures, gastroesophageal reflux disease, dry mouth, weight loss, and rash.

PBC: primary biliary cholangitis; UDCA: ursodeoxycholic acid; ALP: alkaline phosphatase; WI-NRS: Worst Itch Numeric Rating Scale.

Future research should focus on addressing these limitations through comprehensive clinical trials and observational studies. Understanding the full scope of Iqirvo's benefits and risks will be critical in optimizing its use in PBC treatment and ensuring it meets the diverse needs of the patient population.

Conclusion

The accelerated approval of Iqirvo for the treatment of PBC highlights a promising advancement in addressing the unmet medical needs of patients with this chronic liver disease. Clinical trials have demonstrated that Iqirvo significantly reduces alkaline phosphatase levels, providing a potential improvement in liver function for PBC patients. Moreover, Iqirvo exhibits a manageable safety profile, with common adverse effects including gastrointestinal symptoms and pruritus. This approval by the FDA expands the therapeutic options for PBC patients, offering an alternative for those who do not respond adequately to existing treatments such as UDCA.

However, it is crucial to acknowledge that Iqirvo may not be suitable for every patient, and an individualized treatment plan should be considered to optimize outcomes. The continued approval and broader clinical adoption of Iqirvo will depend on further evidence from ongoing and future studies that validate its long-term benefits and safety. Continued research is essential to fully understand the drug's efficacy across diverse patient populations and to explore potential combination therapies that could enhance its therapeutic impact. This ongoing commitment to research will help ensure that Iqirvo fulfills its promise in improving the quality of life and prognosis for patients with PBC.

Ethical approval

Ethical approval is not required for this manuscript.

Consent

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Conflicts of interest disclourse

The authors declare that the research was conducted in the absence of any commercial or financial

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