Editorial

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Elafibranor (Iqirvo) unveiled: a groundbreaking FDA-approved therapy revolutionizing primary biliary cholangitis treatment

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Introduction

Rare hepatobiliary conditions known as autoimmune cholestatic liver disorders are defined by the gradual, inflammatory deterioration of the bile ducts. The two autoimmune cholestatic liver disorders are primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC)[1]. PBC (previously called primary biliary cirrhosis[2]) is a rare and persistent liver disease that destroys the interlobular bile ducts, causing hepatic cholestasis and fibrosis[3]. The average age of presentation is 55 years and is mostly diagnosed in females (92% of cases). PBC is associated with environmental cues, specific geography, family history, and a variety of factors—including nail polish, hair dyes, infectious agents, and smoking—with unknown mechanisms[1]. The labora tory hallmarks of cholestasis are elevated blood levels of alkaline phosphatase (ALP), bilirubin, and gamma-glutamyl transferase (GGT), accompanied by elevated immunoglobulin M concentration[4]. Antimitochondrial antibody (AMA) and the autoreactive CD8 and CD4 T cells are important serological hallmarks of PBC[5]. AMA shows a pattern of being positive in ~90–95% of patients with active PBC[6]. Lastly, cholangiocytes are the active cells of PBC, expressing T-cell ligands that are critical for inducing biliary epithelial autolysis[1].

Past therapeutic approach and associated adverse effects

The nonspecific anticholestatic drug ursodeoxycholic acid (UDCA) happens to be the first-line treatment available for PBC. The ideal dosage is 13–15 mg/kg/day, which is well tolerated[4]. UDCA has several positive effects on cholestatic disorders, including stimulating choleresis and biliary reservoir elevation of hydrophilic bile acids (BA) to 40–50%. It lessens adaptive immunological damage by lowering the biliary and hepatic expression of the MHC class I and II proteins[6]. Even though UDCA transformed PBC care and treated the disease, up to 40% of the population could not benefit from it due to severe diarrhea, flatulence, hair thinning, and weight gain[7].

Obeticholic acid (OCA), the second-line treatment for PBC, is a semisynthetic farnesoid X receptor (FXR) agonist that has anti-inflammatory, antifibrotic, and choleretic properties for individuals with residual cholestasis[4]. When UDCA is insufficient for PBC patients after a year of treatment, OCA is recommended as an adjuvant therapy. Dose-dependent pruritus is a particularly frequent adverse effect of OCA, causing 10–25% of treated people to stop their medication. Furthermore, regardless of dosage, FXR activation by OCA lowers HDL and raises LDL cholesterol, which has a detrimental effect on the lipid panel[8]. OCA happens to be contraindicated in patients with liver cirrhosis and portal hypertension. Another choice of drug for those who do not respond well to UDCA is bezafibrate. Furthermore, individuals with significant portal inflammation may benefit from budesonide. Patients who do not respond well to dual therapy become candidates for triple therapy, which combines bezafibrate, OCA, and UDCA[9]. Inevitably, several negative effects associated with these medications cause a very restricted proportion of people to benefit from them.

Elafibranor: FDA-approved treatment for primary biliary cholangitis

Elafibranor is a drug orally administered, once daily, dual peroxisome proliferator-activated receptors (PPAR) alpha/delta (α, δ) agonist, presently being studied as a potential treatment for patients of PBC, a rare cholestatic liver condition. Elafibranor targets varieties of cells and biological procedures implicated in PBC's pathogenesis by activating PPARα,δ. These processes include bile toxicity, fibrosis and chronic inflammation, cholestasis (deficiency in the liver's bile flow), and the production of bile

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acid[10]. As a PPAR-α/δ agonist, elafibranor (GFT-505) does not contribute to any of the typical cardiac adverse reactions of PPAR-γ ligands. In order to gain medical benefits, it was recommended to evaluate Elafibranor in PBC and is presently being assessed using numerous experiments at medium to substantial doses (80–120 mg/day) as a result of these positive outcomes as well as the noted improvement in hepatic dysfunction indicators[11]. On 10th June 2024, the Food and Drug Administration of the United States approved Elafibranor (iqirvo) to treat PBC based on the outcomes of a double-blinding phase 3 controlled placebo trial[12].

Clinical trials on elafibranor

In a double-blinded phase 2 trial of 12 weeks, 45 patients with PBC that displayed insufficient response to UDCA (ALP levels $\geq$ 1.67-fold the upper limit of normal) randomly received either a placebo, elafibranor 120 mg, or 80 mg. The primary result at 12 weeks was the relative change in ALP. After a 12-week period, ALP decreased in the groups receiving elafibranor 80 mg ($P < 0.001$ compared to placebo) and 120 mg ($P < 0.001$), whereas it increased in the group receiving placebo by $+3.2 \pm 14.8\%$. 67% of patients in the elafibranor 80 mg group and 79% of patients in the elafibranor 120 mg group met the combined objective of total bilirubin levels below the ULN, ALP $\leq$ 1.67-fold the ULN, and ALP decline $> 15\%$, compared with 6.7% of participants in the placebo group. The data Schattenberg *et al.*[13] reported in 2021 demonstrated that elafibranor was effective and tolerated well by PBC patients.

Another global phase 3 double-blinded placebo-controlled trial with 161 individuals having PBC and responding well to the UDCA drug or experiencing unacceptable side effects were randomized (in a 2:1 ratio) and were yet to receive either a placebo or 80 mg elafibranor once daily. The main result depicted a biochemical reaction, which was justified as having typical amounts of total bilirubin and an ALP at week 52 that had reduced by at least 15% from baseline and was below 1.67 times the upper limit of the usual range. Elafibranor caused a biochemical response in 51% of patients (55 out of 108) in comparison with 4% (2 out of 53) who received a placebo[3]. Recent clinical trial on elafibranor is summarized in Table 1.

Table 1

Recent clinical trial on elafibranor.

Clinical trial details	
Title	Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis
Summary	ELATIVE is a multicenter, randomized, double blind, placebo controlled, phase 3 clinical trial that assesses elafibranor's safety alongside effectiveness in subjects with PBC which was compared with the subjects given a placebo
Study type	Relative study
Phase	Phase 3
Disease	Primary Biliary cholangitis
Interventional drugs	Elafibranor, 80 mg dose, or placebo once a day for at least a year
Drug administration	Orally administered
Results	Elafibranor therapy led to noticeably bigger amelioration in pertinent biochemical markers of cholestasis compared to placebo

Mode of action of elafibranor

Elafibranor is a dual agonist acting on the nuclear receptors PPAR α and δ. These receptors control cellular processes related to lipid oxidation, metabolism, and transport of fatty acids. They also impact inflammation and glucose metabolism[14]. Elafibranor decreases hepatic inflammation in addition to enhancing insulin sensitivity, glucose homeostasis, and lipid metabolism[15]. Comparable biochemical markers of cholestasis improved considerably more with elafibranor than under placebo[3].

Pharmacokinetics and pharmacodynamics of elafibranor

When taken orally, elafibranor is rapidly absorbed, with a peak plasma time (Tmax) of about 1.25 h. Elafibranor's peak plasma concentration (Cmax) is 802 ng/ml, and its principal metabolite, GFT1007, reaches a high plasma concentration of 2058 ng/ml at steady state. Elafibranor has an area under the curve (AUC) of 3758 ng·h/ml and GFT1007 has an AUC of 11 985 ng·h/ml, showing the overall drug exposure over time, demonstrating an effective absorption, and substantial systemic exposure of elafibranor[16]. Elafibranor binds to serum albumin to a degree of about 99.7%. Its volume of distribution (Vd) is 4731 L, showing a moderate distribution in body tissues. The cytosolic enzyme prostaglandin reductase (PTGR1) metabolizes elafibranor to generate GFT1007, according to in vitro studies[17]. Elafibranor is eliminated by the kidney[18].

Limitations and adverse effects of elafibranor

While Elafibranor has shown promise in clinical trials, its use is not without limitations. One of the key limitations is the relatively short duration of the phase 2 and 3 trials, which restricts understanding of its long-term safety and efficacy. Furthermore, the biochemical response in 51% of patients, although promising, still leaves nearly half of the patients without a sufficient response, indicating a potential need for combination therapies or alternative treatments.

In terms of adverse effects, Elafibranor's clinical trials reported generally good tolerance, but mild to moderate adverse effects were observed. Some patients experienced gastrointestinal issues, including nausea and diarrhea, which could affect long-term adherence. Additionally, there were reports of transient increases in liver enzymes (ALT and AST), which may raise concerns, especially in patients with more advanced liver disease. Further studies are required to fully assess the drug's impact on lipid profiles, glucose metabolism, and potential interactions with other medications, especially in patients with co-morbidities such as diabetes or cardiovascular disease.

Ultimately, while Elafibranor offers a novel approach for PBC management, its long-term safety profile and full range of adverse effects need to be critically evaluated through extended trials and real-world studies to establish its place in clinical practice.

Future of primary biliary cholangitis and elafibranor

Elafibranor, an oral dual PPAR α and δ agonist, has shown great promise in clinical trials by lowering ALP levels, enhancing the function of the liver, and showing antifibrotic and anti-inflammatory effects—all important aspects of PBC management.

Long-term studies corroborate Elafibranor's sustained safety and effectiveness. Additionally, investigating the combination of therapies with established treatments (OCA and UDCA) also improves therapeutic outcomes. Personalized medicine approaches, which use biomarkers to identify patients who would benefit most from Elafibranor, hold promise for optimizing treatment strategies[3].

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