Editorial

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Latest FDA approved drug Elafibranor (Iqirvo): a novel prospect for treatment of primary biliary cholangitis

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On 10 June 2024, Food and Drug Administration (FDA) approved Elafibranor (Iqirvo, Ipsen Biopharmaceuticals, Inc.) for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) for patients unable to tolerate UDCA or not responsive to UDCA when used alone[1], marking a significant breakthrough in managing this rare debilitating disease.

PBC is a rare autoimmune disorder that causes gradual destruction of intrahepatic bile ducts leading to periportal inflammation and cholestasis, ultimately causing cirrhosis and portal hypertension if left untreated. It is more prevalent in middle aged women (30 to 60 years), with a female to male ratio of 10:1. However, male patients have higher mortality than female patients[2,3]. Prevalence of PBC is higher in North America and Europe than Asian countries[4]. Data on the prevalence of PBC in Pakistan is limited; however, recent studies indicate a prevalence rate of approximately 17.7%[5].

UDCA, a tertiary hydrophilic bile acid, is the first-line drug approved for patients with PBC, however 40% of patients do not respond adequately and experience significant adverse effects[6]. Obeticholic acid, a selective farnesoid X receptor agonist, is approved as a second-line therapy; but less than 50% patients achieve a biochemical response, and it can aggravate pruritus[7]. These limitations of currently available treatment options highlight the pressing need for an effective and better tolerable therapy for patients suffering from PBC.

Elafibranor is a dual peroxisome proliferator-activated receptor (PPAR-α and PPAR-δ) agonist. The exact mechanism of action of Elafibranor in patients with PBC remains unclear. However, therapeutic effects are exerted by activation of PPAR-α and PPAR-δ which modulate the bile acid metabolism. Activation of PPARα inhibits bile acid synthesis (via CYP7A1 suppression), enhances detoxification (through induction of CYP3A4, SULT2A1, or UGT2B4), increases bile acid output (by upregulating BSEP and MRP2), and reduces bile toxicity (by inducing MDR2/3 and ABCG5/G8, which promote phospholipid-rich micelle formation). Both PPARα and PPARδ activation exert anti-inflammatory effects by inhibiting the NF-κB and AP-1 pathways, with PPARδ further demonstrating anti-inflammatory action via the BCL6-mediated pathway[8].

The FDA's approval is based on the promising results witnessed in many clinical trials, notably among them being the ELATIVE (NCT04526665), a multi-center, randomized, double-blind, placebo-controlled study involving 161 patients who were randomized (in a 2:1 ratio) to receive Elafibranor (80 mg) or placebo. Patients treated with Elafibranor demonstrated significantly greater improvement in biochemical response when compared to placebo. Table 1 highlights the important findings of the trial. After 52 weeks of treatment, 51% of patients receiving Elafibranor exhibited decreased cholestasis, compared to only 4% patients taking placebo. Significant decrease in alkaline phosphatase (ALP) was observed in patients who received Elafibranor, signifying good prognosis of the disease. Reduced levels of triglycerides and VLDL and optimal levels of LDL and HDL were noted in patients receiving Elafibranor[9].

Common adverse effects of the drug are abdominal discomfort, nausea, vomiting and diarrhea. Other uncommon adverse reactions were also recorded namely; fractures, elevated creatine phosphokinase levels, myalgia, muscle injury and rhabdomyolysis in patients receiving Elafibranor. New onset cholelithiasis was identified in 3% of patients taking Elafibranor compared to patients who received placebo[9].

Elafibranor may cause fetal harm if administered during pregnancy, as documented by animal studies. Stillbirths, reduced fetal body weight, blue/black discoloration of the caudal section, and developmental delays were observed in pregnant rats treated with Elafibranor. In pregnant rabbits, Elafibranor administration led to significant maternal toxicity, embryo lethality, reduced fetal weight, and a low incidence of fetal malformations. There is inadequate data from human pregnancies exposed to Elafibranor to evaluate the drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Further research is required to investigate its compatibility and efficacy in pregnant women. Hence, caution must be taken before administering the drug in women during pregnancy and lactation. Clinically significant drug interactions of Elafibranor were reported with hormonal contraceptives, HMG-CoA reductase inhibitors, rifampin and bile

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Table 1

Highlights of the ELATIVE trial[a].

Category	Details
Trial Population	Total of 161 patients (108 on Elafibranor, 53 on placebo); intention-to-treat population included 66 patients with moderate-to-severe pruritus (44 on Elafibranor, 22 on placebo)
Patient Demographics	96% female, average age 57 years, baseline ALP level 321.9 U/L
Primary Outcome (Biochemical Response)	Achieved in 51% of Elafibranor group vs. 4% of placebo (difference of 47 percentage points, 95% CI: 32–57; $P < 0.001$), with response noted within 4 weeks
Secondary Outcome (ALP Normalization)	15% normalization in Elafibranor group vs. 0% in placebo group (15 percentage-point difference, 95% CI: 6–23; $P = 0.002$)
Pruritus Score Change (WI-NRS)	Mean reduction: Elafibranor group −1.93 vs. placebo −1.15; difference −0.78 (95% CI: −1.99 to 0.42; $P = 0.20$)
Quality-of-Life Measures	Improvements in itch domains on PBC-40 (difference −2.3; 95% CI: −4.0 to −0.7) and 5-D itch scale (difference −3.0; 95% CI: −5.5 to −0.5)
Sustained ALP Reduction	Sustained ALP reduction in Elafibranor group, with a 40.6 percentage-point decrease relative to placebo (95% CI: −47.8 to −33.5)
Cholesterol Levels	Lower total cholesterol, LDL, VLDL, and triglycerides observed in Elafibranor group by week 4 and maintained through week 52
HDL cholesterol	Stable HDL levels throughout treatment in the Elafibranor group

[a]Kowdley KV, Bowlus CL, Levy C, et al. Efficacy and safety of elafibranor in primary biliary cholangitis. *N Engl J Med.* 2024;390(9):795–805. doi:10.1056/NEJMoa2306185

acid binding sequestrants. Hence, patients taking these drugs must be switched to alternate treatment options and should be closely monitored for any complications[10].

The limitations of the ELATIVE study may impact the interpretation of the efficacy and safety of Elafibranor in broader contexts. The study only included patients without severe hepatic impairment or autoimmune overlap syndromes, which may affect the real-world applicability of results. The predominance of White participants in the study does not address the variability of PBC across different ethnic backgrounds, necessitating future studies with more diverse populations for comprehensive safety and efficacy profiles[9].

The approval of Elafibranor by FDA is an important step forward in the treatment of patients with PBC. Elafibranor has demonstrated significant lowering levels of ALP in patients with PBC, which indicate slower disease progression and improved survival. Sustained ALP normalization is promising for long-term liver health, potentially reducing the progression to cirrhosis and the need for liver transplantation. The side effects reported in the study could hinder long-term adherence, making it critical to assess risk factors in patients for adverse reactions. Additional studies should include a broader range of demographics to better understand safety profile and efficacy across diverse populations. Although PBC is uncommon in Pakistan, the approval of this drug is a significant milestone for patients in limiting disease progression and improving outcomes. Long-term studies are needed to investigate the safety of drug in patients with common comorbidities or those on concurrent treatments, especially given the interaction risks with medications like statins. This novel drug has the capacity to alter the approach towards the treatment of PBC, leading to the development of new drugs and improved care for patients of all age groups. However, more research is needed to evaluate the long-term implications of the drug and to gather detailed insights about its effectiveness over an extended period.

Ethical approval

Not applicable.

Consent

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Author's contribution

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The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest. The authors declare that they have no conflicts of interest.

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Data availability statement

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