EVIDENCE-BASED GI
AN ACG PUBLICATION

Challenges of Full FDA Approval for Obeticholic Acid Based on Reduction of Hepatic PBC Clinical Events

Paul Kwo
Co-Editor-in-Chief

Paul Y. Kwo, MD, FACG

Professor of Medicine and Director of Hepatology, Stanford University School of Medicine, Stanford, CA

HEPATOLOGY

This summary reviews Kowdley KV, Hirschfield GM, Coombs C, et al. COBALT: A Confirmatory Trial of Obeticholic Acid in Primary Biliary Cholangitis With Placebo and External Controls. Am J Gastroenterol. 2025;120 (2):390-400.

Correspondence to Paul Y. Kwo, MD, FACG, Co-Editor-in-Chief. Email: EBGI@gi.org

Keywords: obeticholic acid; primary biliary cholangitis; liver disease; RCT

STRUCTURED ABSTRACT

Question: The goal of this phase 3B/4 study was to determine whether obeticholic acid (OCA) administration could reduce hepatic decompensation events in patients with primary biliary cholangitis (PBC) and advanced liver disease.[1]

Design: This was a prospective randomized controlled study (RCT) combined with a contemporaneous external cohort (EC) of patients derived from a healthcare claims database with 330 million members. The study is registered with ClinicalTrials.gov identifier NCT02308111.

Setting: A RCT in the United States and Europe enrolled patients prospectively. The external cohort was derived from the Komodo Healthcare Map, US health claims database.

Patients: Patients aged ≥18 years diagnosed with PBC were enrolled at 137 sites in 27 countries starting in February 2015. Original entry criteria included mean ALP >5× ULN and mean total bilirubin > ULN and ≤3× ULN. Subsequently, these criteria were revised to ALP >3× ULN and mean total bilirubin > ULN and ≤5× ULN to increase patient recruitment. Eligible patients included those who had either discontinued ursodeoxycholic acid >3 months earlier or who were taking ursodeoxycholic acid >12 months with an approved, stable dose ≥3 months before enrollment. The external cohort used Komodo Healthcare Map, a large US healthcare claims database with approximately 330 million unique patients

Exposure: Patients were randomized to OCA (5–10 mg) were compared with placebo (RCT) or external control (EC)

Outcomes: The primary composite endpoint was time to death, liver transplant, model for end-stage liver disease (MELD) score ≥15, uncontrolled ascites, or hospitalization for hepatic decompensation. A prespecified propensity score–weighted EC group was derived from a US healthcare claims database and analyzed for similar outcomes other than MELD score ≥15.

Data Analysis: In the COBALT RCT, the intention-to-treat (ITT) analysis was a log-rank test of the randomized OCA and placebo cohorts with respect to the primary composite endpoint, stratified by the randomization stratification factors. The EC analysis was a log-rank test of OCA patients in COBALT and comparable non-OCA–treated EC individuals with respect to the primary composite endpoint (excluding MELD score).

Funding: This study was funded by Intercept Pharmaceuticals.

Results: In the RCT, the primary endpoint occurred in 28.6% of OCA (n = 168) and 28.9% of placebo patients (n= 166; ITT analysis hazard ratio [HR]= 1.01, 95% CI 0.68–1.51). Functional unblinding and crossover to commercial therapies occurred, especially in the placebo arm. Correcting for these using inverse probability of censoring weighting and as-treated analyses shifted the HR to favor OCA over placebo. In the EC (n= 51,051), the weighted primary endpoint occurred in 10.1% of OCA and 21.5% of non-OCA patients (HR 50.39; 95% CI 0.22–0.69; *P*=0.001). No new safety signals were identified in the RCT.

COMMENTARY

Why Is This Important?

Ursodiol is effective in the treatment of PBC, although up to 40% of individuals fail to have an adequate response. In 2016, the FDA and EMA granted accelerated approval for OCA as a second-line therapy to treat those with PBC and inadequate response to ursodiol using the surrogate output of reduction of alkaline phosphatase ≤1.67 ULN and normal total bilirubin that was believed to reflect improved survival based on results of the POISE trial.[2] Full approval of OCA was to be based on the long-term confirmatory trial demonstrating improved clinical outcomes in OCA patients with PBC. The COBALT PBC trial was designed to confirm clinical benefit but faced multiple challenges that will likely occur with other therapies that require confirmatory endpoint trials including recently including other recently approved therapies for primary biliary cholangitis (seladelpar and elafibranor) and other in other diseases such as MASH.[3,4]

In the COBALT trial, patients with PBC had more advanced liver disease than those in the initial POISE trial in order to enrich for likelihood of clinical events. However, the data monitoring committee, in conjunction with regulatory authorities, recommended the termination of the study due to the disproportionate exit of patients in the placebo arm. This was due to substantial functional unblinding and initiation of other adjunctive PBC therapies, which occurred at greater rates in the placebo arm than in the OCA arm. This led to a remarkable reduction in alkaline phosphatase in the placebo arm of the COBALT trial, with no difference in hepatic events being demonstrated between the OCA and placebo arms in the ITT analysis. The EC analysis demonstrated reduced primary endpoints in the OCA-treated arm compared to untreated controls, a result that has been replicated in other real-world cohorts[5]

Key Study Findings

EC analysis demonstrated that OCA treatment is associated with a significant reduction in risk of negative clinical outcomes. Confounding in the RCT ITT analysis demonstrates the value of EC data in confirmatory trials of rare diseases.

Caution

The high dropout rate greatly influenced the negative findings of the randomized trial. Based on these results, the FDA advisory panel declined to grant long-term approval for OCA for non-responders to PBC first-line therapy. The external cohort in the setting is beneficial in that the response rates appear comparable to other PBC non-responder trials and represent an attractive option to generate post-conditional approval data confirming long-term benefits and clinical outcomes. High dropout rates may be a challenge for all

therapies that will be conducted in populations with more advanced liver disease who are at risk for decompensation, liver transplant, hepatocellular carcinoma, and death. Indeed, many physicians may choose not to put these at-risk patients in clinical trials even though these are the populations where the therapeutic intervention will likely demonstrate the greatest benefit.

There is not a regulatory approval pathway yet finalized using real-world evidence to confirm clinical outcome efficacy.

My Practice

OCA was the first approved second-line therapy for PBC based on the POISE trial. Recently 2 therapies have been approved as second line therapy for PBC. Both seladelpar and elafibranor have also been shown to meet their primary endpoint, including a reduction in alkaline phosphatase to less than 1.67 times the upper limit of normal. These therapies now must also undergo similar prospective trials to determine whether these therapies can also prevent clinical decompensation and improve long-term outcomes in those with primary biliary cholangitis and will face similar challenges of the COBALT trial, particularly in those with advanced liver disease who must remain on placebo. OCA should no longer be used in those with advanced cirrhosis and portal hypertension due to an FDA safety update, and compared to seladelpar and elafibranor, does not have the same improvement in pruritus. I have been utilizing the newer agents for my PBC patients who require adjunctive therapy, and offer those who are responding and tolerating OCA therapy well the option to transition to these agents, though there is no data that seladelpar and elafibranor are effective in treating those who have responded to OCA as a second line therapy.

For Future Research

An important priority is for drug developers, investigators, and regulatory authorities is to come together to address the challenges of conducting confirmatory trials in those with advanced liver disease where placebo arms are highly likely to fail as occurred in the Coldwell trial. The EMA has recently released initial guidance about this issue with a potential path forward[6], and it is hoped that the FDA will also address this important issue.

Conflict of Interest

Dr. Kwo has the following disclosures: Consultant for Abbvie, Durect, Genentech, HepQuant, Inventiva, LyGenesis, Madrigal, Mirum, PB Gene, Tune Therapeutics; advisory board member for Aligos, Amgen, Arbutus, Galapagos, Gilead, Mallinckrodt, Novo Nordisk, Ocelot, and Surrozen; research support from Altimmune, Ausper Bio, Inventiva, Novo Nordisk, Salix, Takeda, Target Registries, and Ultragenyx.

Abbreviations

ALP, alkaline phosphatase; CI, confidence interval; EC, external cohort; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HR, hazard ratio; MELD, model for end-stage liver disease; OCA, obeticholic acid; PBC, primary biliary cholangitis; RCT, randomized controlled trial; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

REFERENCES

1. Kowdley KV, Hirschfield GM, Coombs C, et al. COBALT: A confirmatory trial of obeticholic acid in primary biliary cholangitis with placebo and external controls. *Am J Gastroenterol* 2025; 120(2): 390-400.
2. Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med*. 2016;375(7):631-643.
3. Hirschfield GM, Bowlus CL, Mayo MJ, et al. A phase 3 trial of seladelpar in primary biliary cholangitis. *N Engl J Med.* 2024;390(9):783-794.
4. 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.
5. Perez CFM, Fisher H, Hiu S, et al. Greater transplant-free survival in patients receiving obeticholic acid for primary biliary cholangitis in a clinical trial setting compared to real-world external controls. *Gastroenterology.* 2022;163(6):1630-1642. e3.
6. European Medicines Agency. Reflection paper on regulatory requirements for the development of medicinal products for primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). EMA/CHMP/299976/2018. Published December 19, 2023. Accessed April 15, 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-requirements-development-medicinal-products-primary-biliary-cholangitis-pbc-primary-sclerosing-cholangitis-psc_en.pdf