Long-term obeticholic acid (OCA) for Primary Biliary Cholangitis (PBC) in a clinical trial improved event-free survival (death, liver transplant, and hepatic decompensation) compared to external controls from the Global PBC real-world database

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Introduction

- Primary biliary cholangitis (PBC) is a rare autoimmune cholestatic liver disease primarily affecting women >40 years of age.[1,2] Without treatment, patients can progress to end-stage cirrhosis, hepatic decompensation, and death.[3]
- The POISE 12-month randomized, double-blind placebo-controlled trial investigated obeticholic acid (OCA) as 2nd line therapy in patients inadequately responding (ALP>1.67xULN and/or total bilirubin >ULN but <2xULN) or intolerant to ursodeoxycholic acid (UDCA).[4]
  - Patients were randomized to placebo, OCA 5mg titrated to 10mg, or OCA 10mg.
  - At 12 months, 46% of patients in the OCA 5mg – 10mg group achieved ALP reduction below 1.67xULN and normal total bilirubin vs 10% in the placebo group.
  - After 12 months, patients were transferred to an Open Label Extension (OLE) and treated with OCA 5mg – 10mg and followed for up to 5 additional years.
- OCA received accelerated regulatory approval for PBC based on biomarker improvement in the POISE trial.
- Currently, no placebo controlled long-term outcomes data exists for 2nd line therapy in PBC. Availability of follow-up data in a large registry presents an opportunity to build a rigorous external control (EC) cohort that can be compared to OCA treated patients in clinical trails and the real world.
- The objective of this study was to evaluate the long-term efficacy of OCA based on first occurrence of death, liver transplant, or hepatic decompensation among OCA-treated patients in the POISE trial compared to a comparable non-OCA-treated EC.

Methods

Population

- The treatment arm included patients in the POISE 12-month randomized controlled trial and 5-year OLE study. The EC cohort included OCA-naive patients from the Global PBC registry diagnosed with PBC, treated or untreated with UDCA, with > 1 year of follow-up, and met POISE study inclusion criteria.

Endpoint

- Time to first occurrence of hepatic decompensation, liver transplant, or death.

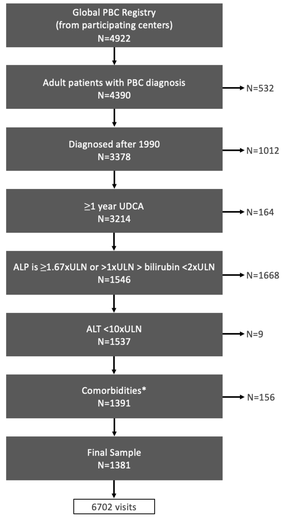
Analysis

- As treatment was not assigned randomly, baseline variables could influence both the chances of a clinical event and of receiving treatment. To ensure a fair and balanced comparison, inverse probability of treatment weighting (IPTW) was used to balance groups.
- For the EC cohort, an index date was randomly selected from all visits on which a patient met all POISE eligibility criteria but was not treated with OCA.
- Logistic regression was used to create propensity scores, with treatment (OCA vs EC) as the outcome and the following predictors: age, sex, calendar year of diagnosis, PBC duration, UDCA use, ALP, bilirubin, and AST or ALT. IPTWs were then calculated for each patient.
- Cox proportional hazards models were used to determine hazard ratio (HR) and 95% confidence intervals.
- A secondary analysis examined the impact of adding cirrhosis to the model.

Results

- POISE inclusion criteria were met by 1381 patients in the Global PBC registry, with 6702 qualifying visits (Figure 1) from which 1 index was randomly selected per patient.
- Unweighted baseline characteristics are shown in Table 1.
- Standardized variable differences before and after weighting show that all variables were within the pre-specified ± 0.25 standardized mean difference (SMD) and the samples were comparable after weighting (Figure 2).

Figure 1. Global PBC Cohort Derivation Based on Exclusions to Match POISE Cohort



*History of spontaneous peritonitis, variceal bleeding, ascites, encephalopathy, or hepatocellular carcinoma within the first 6 months.

Figure 2. Standardized Variable Differences Before and After Weighting

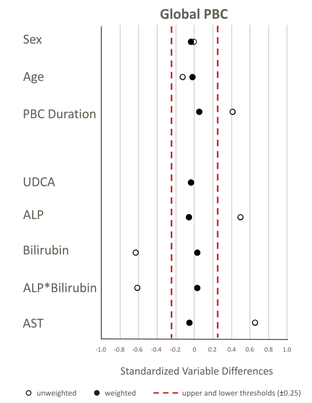


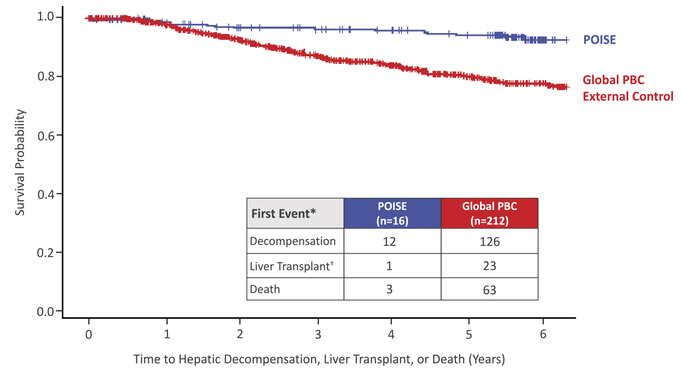
Table 1. Baseline (Unmatched) Characteristics of the POISE OLE and Global PBC Cohorts

	POISE OLE (n=209)	Global PBC (n=1381)
Female, n (%)	190 (90.9)	1253 (90.7)
UDCA, n (%)	197 (94.3)	1265 (91.6)
Year of diagnosis, median (IQR)	2005 (2000-2009)	1999 (1994-2003)
Year of visit median (IQR)	2012 (2012-2012)	2005 (2000-2009)
Age, years, mean (SD)	55.7 (10.6)	56.9 (12.3)
Duration of disease, years, median	7.8 (3.6-12.6)	4.5 (2.1-7.9)
ALP, ×ULN, median (IQR)	2.41 (2.00-3.15)	2.08 (1.75-2.81)
Bilirubin, ×ULN, median (IQR)	0.47 (0.34-0.67)	0.67 (0.45-1.09)
AST, ×ULN, median (IQR)	1.68 (1.20-2.36)	1.20 (0.88-1.78)
ALT, ×ULN, median (IQR)	2.09 (1.44, 3.02)	-
Cirrhosis at inclusion, n (%)	36 (17.2)	197 (14.3)

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; IQR, inter-quartile range; OLE, open-label extension; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

- Over the 6.3 years of follow-up, there were 16 events of hepatic decompensation, liver transplant, or death in 209 subjects in the POISE arm (Incidence rate (IR) 18.0 per 1,000 person-years; 95% CI 10.7, 28.6) and 212 events in 1381 patients (IR 35.5 per 1,000 person-years; 95% CI 31.0, 40.5) in the Global PBC external control group.
- The IPTW HR=0.42 (95% CI 0.21, 0.85; p=0.02), indicating that patients treated with OCA in a trial setting had significantly greater event-free survival than patients in the Global PBC control group (Kaplan-Meier curve is shown in Figure 3).
- The Cox regression was run separately for patients with and without cirrhosis. Widely overlapping confidence intervals indicated no significant difference in outcomes for OCA treated patients with cirrhosis compared to Global PBC controls (HR=0.38; 95% CI 0.12, 1.20) versus OCA treated patients without cirrhosis (HR=0.34; 95% CI 0.14, 0.82) (Figure 4).

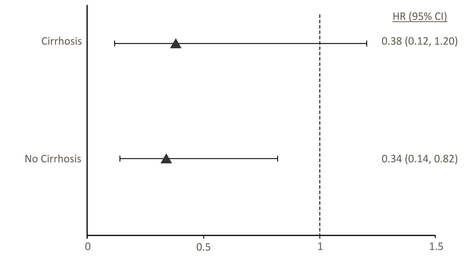
Figure 3. Event-free Survival Comparing POISE to the Global PBC External Control Arm



First Event*	POISE (n=16)	Global PBC (n=212)
Decompensation	12	126
Liver Transplant†	1	23
Death	3	63

* Event rates represent the first event occurring in patients who had multiple events recorded.
† To assess liver transplants, all POISE libraries (raw data, clinical study report listings, Analysis Data Model (ADaM) and Study Data Tabulation Model (SDTM)) for both the double-blind and OLE phases were programmatically searched for the strings "liver" AND "trans". The search was conducted by 2 investigators and results reconciled. This search was conducted after initial results were reported at AASLD 2021.

Figure 4. Hazard Ratios for POISE vs Global PBC External Controls by Cirrhosis Status



Conclusions

- Patients treated with OCA in this trial setting demonstrated a statistically significant and clinically meaningful 58% relative risk reduction over a 6-year time period for the composite endpoint of hepatic decompensation, liver transplant, or death compared to non-OCA treated patients in the Global PBC registry.
- Reduction in risk was independent of presence or absence of cirrhosis.
- These results support the use of long-term OCA therapy to optimize prognosis of patients with PBC inadequately responding or intolerant to UDCA.

References

1. Lleo et al. Lancet. 2020;396:1915-1926.
2. Trivedi et al. Gut. 2021;70:1989-2003.
3. Hohenester et al. Semin Immunopahtol. 2009;31:283-307.
4. Nevens et al. NEJM. 2016;375:631-643.

Acknowledgements

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