Primary Biliary Cholangitis (PBC) in the U.S.: Real World Effectiveness of Obeticholic Acid in TARGET-PBC

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INTRODUCTION

- Primary biliary cholangitis (PBC) is an uncommon autoimmune cholestatic liver disease.
- Up to 40% of PBC patients do not achieve a complete biochemical response to ursodeoxycholic acid (UDCA).
- Obeticholic acid (OCA) was approved by the FDA in 2016 for PBC patients not responding or intolerant to UDCA.

METHODS

- TARGET-PBC is an observational study, initiated in 2016, of adult patients with PBC managed at 25 academic and community Hepatology and Gastroenterology practices.
- Treatment of PBC and initiation of OCA is at the discretion of the treating physician. Patient management will follow each site's local standard of care and no specific treatments, clinical assessments, or laboratory tests will be dictated by enrollment in the study.
- Enrollment after May 2017 was enriched to include only those with elevated serum alkaline phosphatase (ALP) despite UDCA therapy or those treated with OCA or fenofibrate (47% of current enrollment).
- Cirrhosis is derived based on any of the following: stage 4 fibrosis on biopsy, stage 3 fibrosis on biopsy and one secondary condition, two secondary conditions, or stiffness >= 17 on FibroScan.
  - Secondary conditions include portal hypertension, ascites, varices or collaterals, platelets < 140, cirrhosis on other imaging, and splenomegaly.
- Decompensated requires ascites, encephalopathy, variceal bleeding, or Child-Pugh B or C.

PARTICIPANT CHARACTERISTICS

Total enrollment to date for TARGET-PBC is 405 participants with evaluable data from 63 participants that have ever been prescribed OCA. The age, duration of disease and gender are similar to the baseline characteristics from the POISE trial.

Participant Characteristics at Study Entry (n=63)	
Median Age at Study Entry	56 years
Mean Duration of Disease	7.7 years (1 to 25 years)
Gender	92.1% Female (n=58)
Race	81.0% Caucasian (n=51)
Ethnicity	20.6% Hispanic (n=13)
AMA Positive	84.7% (n=50)
Mean Duration of OCA Treatment	10.7 months (1 – 37 months)
Mean UDCA Dose[1]	16.3 mg/day
Autoimmune Hepatitis Overlap	19.0% (n=12)
Cirrhosis	55.6% (n=35)
Mean Child Pugh Score for Cirrhotic	6.0 (5 – 12)
Decompensated Cirrhotic	48.6% (n=17)
Mean Child Pugh Score for Decompensated Cirrhotic	8.0 (5 – 12)

[1]One participant discontinued UDCA due to intolerance

STATEMENT & DISCLOSURES

TARGET-PBC is a collaboration among academic & community investigators, the pharmaceutical industry, and PBC patient community advocates. TARGET-PBC is sponsored by TARGET PharmaSolutions, Inc. TARGET thanks the study staff, nurses, health care providers and patients at each study center for their contributions to this work. Listings of Principal Investigators and Industry Partners are available upon request by emailing info@targetpharmasolutions.com.

Cynthia Levy, MD Disclosures: Consultant for Intercept, Novartis, GSK, Cara Therapeutics, TARGET PharmaSolutions; Research Grants from Intercept, Novartis, GSK, Gilead, Genfit, CymaBay, Durect, HighTide, Alnylan, Enanta, Genkyotek.

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LABORATORY VALUES

Last available pre-OCA laboratory values were compared to the last available post start of OCA laboratory values. All laboratory values are based upon site specific local laboratory values.

- 77.4% (n=41) of participants experienced a drop in ALP
  - 60.4% (n=32) of participants experienced a drop in ALP >15%
  - 22.6% (n=12) participants experienced a drop in ALP to < 1.5 ULN
- 81.1% (n=43) of participants experienced a drop in ALT
- 78.8% (n=41) of participants experienced a drop in AST

Laboratory Values	Mean Pre-OCA	Mean Post-OCA	Mean % Change	P-Value
Alkaline Phosphatase (ALP)	381 IU/L (All) 412 U/L (LC) 338 IU/L (Non-LC	265 IU/L (All) 290 IU/L (LC) 233 (Non-LC)	-21.5% (All) -22.7% (LC) -20.0% (Non-LC)	<.0001 (All) <.0001 (LC) .0030 (Non-LC)
Alanine Aminotransferase (ALT)	62.0 IU/L (All) 69.5 IU/L (LC) 51.4 IU/L (Non-LC)	48.0 IU/L (All) 47.3 IU/L (LC) 49.0 IU/L (Non-LC)	-18.8% (All) -26.3% (LC) -8.16% (Non-LC)	<.0001 (All) <.0001 (LC) .1433 (Non-LC)
Aspartate Aminotransferase (AST)	62.9 IU/L (All) 74.7 IU/L (LC) 46.8 IU/L (Non-LC)	52.1 IU/L (All) 57.6 IU/L (LC) 45.2 (Non-LC)	-14.5% (All) -21.0% (LC) -5.62% (Non-LC)	<.0001 (All) <.0001 (LC) .1528 (Non-LC)
Total Bilirubin (TB)	1.45 mg/dL (All) 1.90 mg/dL (LC) 0.84 mg/dL (Non-LC)	1.63 mg/dL (All) 2.03 mg/dL (LC) 1.13 mg/dL (Non-LC)	4.29% (All) -4.12% (LC) 15.77% (Non-LC)	.9189 (All) .4354 (LC) .3833 (Non-LC)
Platelets	204.4 10^3/uL (All) 171.5 10^3/uL (LC) 250.1 10^3/uL (Non-LC)	188.8 10^3/uL (All) 143.1 10^3/uL (LC) 245.4 10^3/uL (Non-LC)	-6.3% (All) -12.5% (LC) 2.2% (Non-LC)	.0095 (All) .0003 (LC) .9661 (Non-LC)
Albumin	4.0 g/dL (All) 3.8 (LC) 4.1 (Non-LC)	3.8 g/dL (All) 3.6 g/dL (LC) 4.1 g/dL (Non-LC)	-3.59% (All) -5.37% (LC) -1.04% (Non-LC)	.0700 (All) .0325 (LC) .8730 (Non-LC)
Creatinine	0.73 mg/dL (All) 0.72 mg/dL (LC) 0.73 mg/dL (Non-LC)	0.73 mg/dL 0.72 mg/dL (LC) 0.74 (Non-LC)	10.05% (All) 17.73% (LC) -1.05% (Non-LC)	.7060 (All) .8124 (LC) .7819 (Non-LC)
INR	1.02 (All) 1.03 (LC) 0.97 (Non-LC)	1.09 (All) 1.14 (LC) 1.00 (Non-LC)	6.65% (All) 8.18% (LC) 3.02% (Non-LC)	.2410 (All) .3470 (LC) .8750 (Non-LC)

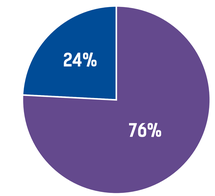
LC = Liver Cirrhosis

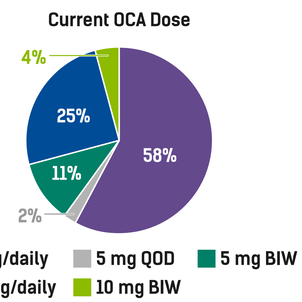
PARTICIPANTS WITH ABNORMAL BILIRUBIN

Most participants (42/52, 80.8%) had normal total bilirubin (TB) prior to OCA start and remained essentially unchanged during treatment. Ten participants (19.2%) had elevated TB prior to start of OCA.

	Pre-OCA TB	Post-OCA TB	Continued Treatment	Current OCA Dose	Listed For Transplant	Reason for OCA Discontinuation
1	2.0 mg/dL	2.0 mg/dL	Yes	5.0 mg QD	No	
2	2.1 mg/dL	1.5 mg/dL	No		No	Discontinued OCA due to pruritus
3	2.4 mg/dL	2.3 mg/dL	No		No	Discontinued OCA due to pruritus
4	2.5 mg/dL	0.7 mg/dL	Yes	5.0 mg QD	No	
5	2.6 mg/dL	4.2 mg/dL	Yes	10 mg BIW	No	
6	2.6 mg/dL	4.8 mg/dL	No		No	Discontinued OCA due to elevation in TB
7	3.5 mg/dL	11.5 mg/dL	No		No	Discontinued OCA due jaundice and potential for acute drug injury
8	3.6 mg/dL	4.9 mg/dL	No		No	Discontinued OCA due to lack of efficacy
9	9.6 mg/dL	7.2 mg/dL	No		No	Discontinued OCA due to pruritus
10	10.6 mg/dL	15.1 mg/dL	Yes	5.0 mg BIW	No	

OCALIVA DOSING





Reasons for OCA Discontinuation	
Adverse Events	17.5% (n=11) 63.6% of the adverse events were pruritus
Financial Reasons	3.2% (n=2)
Clinical Trial Ended	1.6% (n=1)
Lack of Efficacy	1.6% (n=1)

ADVERSE EVENTS*

Adverse events are defined as any new medical event, regardless of causality, captured in the medical records after the start of OCA.

Pruritus 25.4% (n=16)	Back pain 4.8% (n=3)	Depression 3.2% (n=2)	Oedema peripheral 3.2% (n=2)
Fatigue 12.7% (n=8)	Dry Eye 4.8% (n=3)	Elevated liver enzymes 3.2% (n=2)	Pyrexia 3.2% (n=2)
Abdominal Pain 9.5% (n=6)	Insomnia 4.8% (n=3)	Haemorrhoids 3.2% (n=2)	Vertigo 3.2% (n=2)
Constipation 6.3% (n=4)	Gastroesophageal reflux disease 4.8% (n=3)	Hypokalaemia 3.2% (n=2)	Vitamin D deficiency 3.2% (n=2)
Osteopenia 6.3% (n=4)	Anaemia 3.2% (n=2)	Nasopharyngitis 3.2% (n=2)	Vomiting 3.2% (n=2)
Urinary Tract Infection 6.3% (n=4)	Arthralgia 3.2% (n=2)	Nausea 3.2% (n=2)	

CONCLUSIONS

- The participants in the TARGET-PBC cohort were more advanced than those studied in POISE, the randomized clinical trial (RCT) for OCA approval; here, 19% had AIH overlap, >50% had Cirrhosis, almost a third of all patients had decompensated cirrhosis.
- The results in this more advanced population are consistent with the POISE RCT results and use of OCA had a beneficial effect on the biochemical endpoints.
- TARGET-PBC participants with the most advanced disease (BL bilirubin over 2mg/DL), 5 improved/stayed the same; 5 worsened/stayed the same; none advanced to LT.
- In participants without cirrhosis, platelet count and albumin tended to stay stable, but in participants with cirrhosis trended towards deterioration, suggesting that earlier intervention before cirrhosis might be more beneficial to slow progression.
- The frequency of pruritus was lower than reported in the POISE clinical trial. However, the rate of treatment discontinuation we reported is higher, likely because of the more advanced disease population in this cohort.
- Better education of providers on management of pruritus while on OCA may improve drug tolerance and help reduce drug discontinuation.