A Real-World Observational Cohort of Patients With Primary Biliary Cholangitis: TARGET-Primary Biliary Cholangitis Study Design and Rationale

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Primary biliary cholangitis (PBC) is a rare chronic cholestatic liver disease that may progress to biliary cirrhosis if left untreated. The first-line therapy for PBC is ursodeoxycholic acid (UDCA). Unfortunately, 1 of 3 patients does not respond to UDCA. These patients are at risk for developing clinical events, including cirrhosis, complications of portal hypertension, hepatocellular carcinoma, liver transplant, or death. Recently, the U.S. Food and Drug Administration approved obeticholic acid to be used in certain patients with PBC. Off-label therapies are also used, and several other therapies are currently under evaluation. Real-world effectiveness of newly approved and off-label therapies remains unknown. TARGET-PBC is a 5-year, longitudinal, observational study of patients with PBC that will evaluate the effectiveness of clinical practice interventions and provide practical information unobtainable in registration trials. Enrollment will take place at both academic and community sites. In addition to consenting to medical records review, participants will be asked to provide an annual blood sample and complete patient reported outcome surveys at predetermined intervals. Any available liver biopsies will be digitally preserved. *Conclusion:* Key study outcomes will be the evaluation of the safety and effectiveness of PBC interventions and the assessment of disease progression under real-world conditions. (*Hepatology Communications* 2018;2:484-491)

Primary biliary cholangitis (PBC), formerly called primary biliary cirrhosis, is an uncommon chronic cholestatic liver disease characterized by progressive inflammation and destruction of the interlobular bile ducts, ultimately leading to the development of biliary cirrhosis. The incidence across Europe, North America, Asia, and Australia has been estimated to range from 0.9 to 5.8 per 100,000 people, with a prevalence range from 1.91 to 40.20 per 100,000 people.[1] Approximately 130,000 individuals

in the United States may have the disease.[2] PBC most often affects middle-aged women and can significantly diminish their quality of life by causing symptoms such as pruritus and fatigue as well as leading to liver failure. The natural history of untreated PBC is one of slow progression toward cirrhosis, with median survival without liver transplantation ranging from 10 to 15 years.[3]

Ursodeoxycholic acid (UDCA), approved by the U.S. Food and Drug Administration (FDA) in 2004 as a first-line therapy for PBC, is a hydrophilic bile acid, and most published therapeutic trials on its use in patients with PBC have shown positive effects on biochemical parameters and histologic variables.[4] Specifically, at a dose of 13-15 mg/kg/day, UDCA has been shown to improve biochemical liver tests, delay development of fibrosis, delay the rate of development of esophageal varices, and prolong survival without liver transplantation in patients with PBC.[5,6] Definitions of biochemical response to therapy have continued to be proposed and to evolve (Table 1).[3] The GLOBE score is a validated risk calculation developed by the Global PBC Study Group that reliably predicts response to UDCA using five objective variables (age, bilirubin, albumin, alkaline phosphatase [ALP], and platelet count). Comparison to a similar age-matched control population allows identification of patients for whom monotherapy with UDCA is inadequate and who will benefit most from new therapies. The ALP and total bilirubin values in particular show strong predictive significance. The GLOBE score predicts prognosis (survival and transplant-free survival) of patients who have been treated with UDCA for 1 year, regardless of their disease stage, and helps to direct therapeutic decisions.[7] Transplant-free survival can also be accurately calculated using the GLOBE score with laboratory values collected 2-5 years after UDCA treatment. Importantly, the GLOBE PBC risk score was also validated in patients who were not taking UDCA.

Regardless of the classification and scoring systems, up to 40% of treated patients fail to reach biochemical response to UDCA. Poor biochemical response clearly correlates with diminished survival and need for liver transplantation. Developing an alternative medical strategy for incomplete responders is therefore of utmost importance.

A variety of other drugs have been studied in PBC with little or no added benefit to UDCA. These have included immunosuppressants, immunomodulators, antifibrotics, antioxidants, antibiotics, and even antivirals. Budesonide and fibrates are under investigation as additional treatment options. In patients with incomplete response to UDCA (13-15 mg/kg/day), the addition of 160 mg of daily fenofibrate has been found to further biochemical improvement in terms of serum ALP, aspartate aminotransferase. and immunoglobulin M levels.[3] Fenofibrate has been used as off-label treatment for PBC. Likewise, the recent randomized controlled study of bezafibrate in combination with UDCA in primary biliary cirrhosis (BEZURSO) trial showed that bezafibrate led to normalization of serum ALP in 67% of PBC patients with inadequate response to UDCA.[8] This medication, however, is not available in the United States.

Obeticholic acid (6-alpha-ethyl-chenodeoxycholic acid; OCA) is a farnesoid X receptor agonist and is the second FDA-approved treatment for PBC. The phase III PBC OCA International Study of Efficacy (POISE) demonstrated that 12 months of OCA, administered either as adjuvant to UDCA or alone, resulted in improvements in ALP, total bilirubin, and other biochemical markers of disease.[9] Subsequently, in May 2016, the FDA approved OCA to be used in combination with UDCA for patients with PBC and an incomplete response to UDCA or as monotherapy for those who are intolerant to UDCA.[10]

Importantly, phase III clinical trials are performed in highly selected adherent study participants who may

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TABLE 1. DEFINITIONS OF BIOCHEMICAL RESPONSE TO UDCA IN PBC

Criteria	Definition
Paris I	ALP <3 times ULN, aspartate aminotransferase <2 times ULN, and bilirubin ≤1 mg/dL after 1 year of UDCA
Barcelona	ALP decline of >40% toward baseline value or a normal level after 1 year of UDCA treatment
Rotterdam	Normalization of bilirubin and albumin concentrations after treatment with UDCA when one or both parameters were abnormal before treatment or normal bilirubin or albumin concentrations after treatment when both were abnormal at entry
Paris II	ALP and aspartate aminotransferase ≤1.5 times ULN and normal total bilirubin after 1 year of UDCA therapy
Toronto	ALP <1.67 times ULN at 2 years of UDCA therapy
GLOBE PBC	Age (years) at initiation of UDCA therapy and total bilirubin, alkaline phosphatase level, albumin, and platelets after 1 year of therapy are compiled to produce an age and sex-matched score. Globe score >0.3 indicates shortened survival free of liver transplantation compared to controls.
United Kingdom-PBC	Total bilirubin, alanine transaminase/aspartate transaminase, and ALP compared to ULN and serum albumin and platelet count compared to LLN after at least 12 months of UDCA therapy

Abbreviations: LLN, lower limit of normal; ULN, upper limit of normal.

lack significant comorbidities outside the disease area in question. This has been the case in several areas within hepatology.[11] These trials are good measures of clinical efficacy; however, the more germane question for clinicians and their patients is one of real-world effectiveness. Confirming the safety and effectiveness of interventions under real-world conditions and establishing pragmatic methods of assessing disease diagnosis and progression are critical for developing appropriate clinical practice guidelines. This assessment can only be made in postmarketing surveillance when new medications are incorporated into general practice among patients with multiple comorbidities and variable levels of treatment compliance. Ongoing monitoring of side-effect profiles of these emerging therapeutic agents for PBC and determination of whether proposed management plans within clinical trial protocols are effective in mitigating adverse events in clinical practice are essential for guiding policies on PBC management.

TARGET-PBC is a cooperative consortium of principal investigators from both academic institutions and community sites that treat patients with PBC. It will provide unique opportunities to engage networked physician teams in evidence-based evaluation of PBC therapies and to involve these teams in clinical research. This collaboration of expertise and the information gathered from specimen-banking high-throughput technologies and biomedical informatics will allow investigators to analyze data at a variety of levels, from subsets to very large populations.

Patients and Methods

OVERVIEW

TARGET-PBC is a 5-year, longitudinal, observational study that will describe the real-world practice of

diagnosis, management, and natural history of PBC. The overarching aim of TARGET-PBC is to demonstrate the clinical effectiveness of PBC therapies in a real-world setting. It uses standardized data collection tools and follows a detailed protocol to increase the efficiency and minimize costs associated with performing clinical research, while ensuring collection of critical safety and efficacy data on prescribed PBC therapies. Adult (≥18 years old) patients being managed or treated for PBC are included. Up to 1,500 adults with PBC will be enrolled. Current participating patients are from academic (n = 16) and community (n = 2) gastroenterology and hepatology practices and represent a national distribution (Fig. 1). 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. Site recruitment is ongoing. Central and/or local institutional review board (IRB) approvals are obtained prior to patient enrollment. The entire study will be conducted in accordance with good clinical practice requirements and compliance with the ethical principles described in the current revision of the Declaration of Helsinki.

INCLUSION/EXCLUSION CRITERIA

As this study seeks to reflect real-world clinical practice, patients may be enrolled if they are being managed or treated for PBC, regardless of which treatment they are receiving. The diagnosis of PBC is made by the treating physician to reflect real-world practice. Patients are excluded if they are unable to provide written informed consent and/or are simultaneously enrolled in another prospective registry or clinical trial or study where PBC treatment outcomes are reported
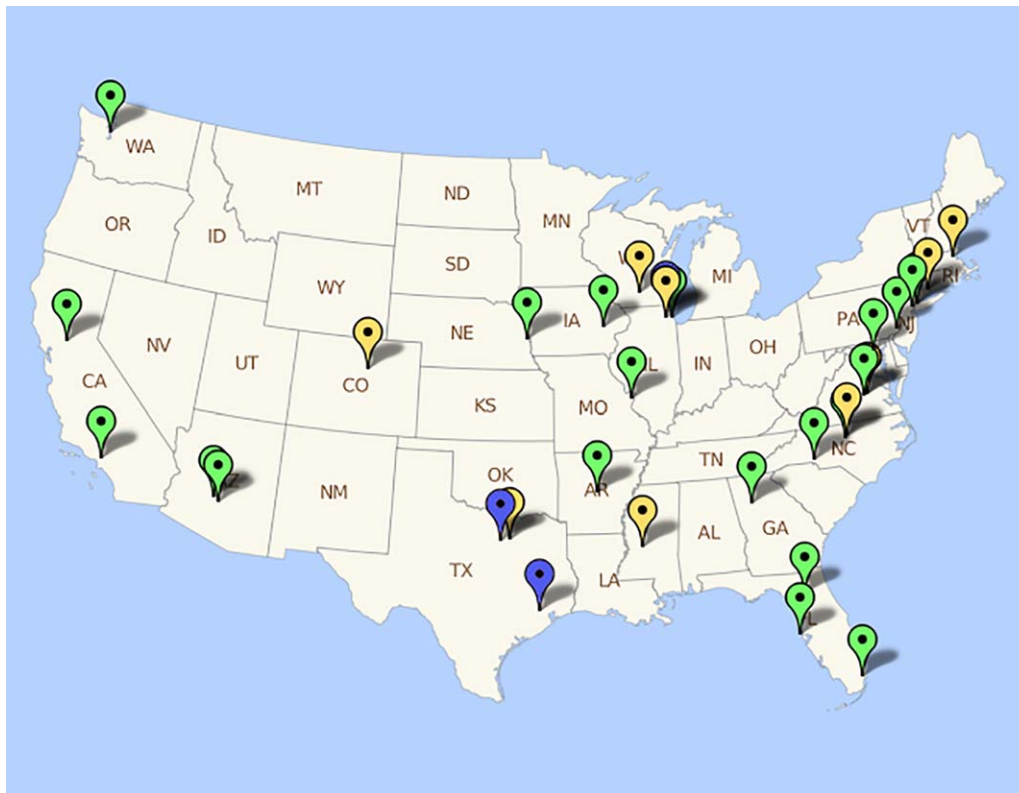
FIG. 1. US map of TARGET-PBC participating sites at the moment of manuscript submission. Green, sites that are actively enrolling patients; yellow, sites in start-up stage; blue, sites in feasibility stage.

(except where approved or conducted as an adjunct project of TARGET-PBC).

To improve our ability to detect clinically relevant events during the 5-year follow-up period and given that UDCA has been well studied for decades, an amendment to the study protocol for targeted enrollment was generated to enrich the study population with UDCA nonresponders and UDCA-intolerant patients. This strategy allows us to focus on at-risk patients and to better understand how new therapies impact outcomes in PBC.

OUTCOMES OF INTEREST

The primary and secondary aims of the study are listed in Table 2 and include mainly the evaluation of effectiveness and safety of various treatment regimens for PBC. This includes use of off-label medications, such as fenofibrate, and immunosuppressants, such as budesonide, mycophenolate mofetil, and tacrolimus. Additional outcomes of interest include disease

progression (i.e., worsening of fibrosis, incident cirrhosis, and cirrhosis decompensation events) and medication effectiveness in special populations (Table 3) unlikely to be represented in clinical trials. With respect to comorbidities, we are particularly interested in studying the impact of associated autoimmune

TABLE 2. PRIMARY AND SECONDARY AIMS OF TARGET-PBC

Primary aims	• Evaluate PBC treatment regimens being used in clinical practice
	• Examine outcomes in populations underrepresented in phase III clinical trials
	• Examine biochemical response to various treatment regimens and its association with long-term outcomes
	• Estimate adverse event frequency and severity and describe management practices
Secondary aims	• Describe response rates and safety in special populations
	• Determine safety and efficacy of unapproved regimens
	• Evaluate drug–drug interactions
	• Evaluate health outcomes and durability of clinical response
	• Evaluate patient reported outcomes measures

TABLE 3. SPECIAL POPULATIONS EVALUATED IN TARGET-PBC

- Patients with cirrhosis, compensated or not
- Patients before and after liver transplant
- Patients with comorbidities
- Patients with other coexisting liver disease, such as autoimmune hepatitis (overlap syndrome), nonalcoholic fatty liver disease, alcoholic liver disease, or viral hepatitis
- Patients using concomitant medications that were excluded in clinical trials, such as various immunosuppressants, biologicals, fibrates, and corticosteroids

hepatitis (overlap syndrome autoimmune hepatitis-PBC), other autoimmune diseases, and metabolic syndrome on the course of PBC. With our data set, we will also be able to evaluate the impact of sex, race/ethnicity, and comorbidities on the progression of PBC.

STUDY PROCEDURES

After informed consent is obtained, redacted medical records for the previous 3 years are gathered. Structured and unstructured data are then extracted for medication use, comorbid conditions, imaging tests, endoscopic procedures, surgeries, and pathology. Patients who have consented to complete optional patient reported outcome (PRO) surveys will do so every 6 months as outlined below (Table 4). Patients who have consented to be part of the Biorepository Specimen Bank will have blood collected during regular clinical blood work for DNA/RNA and serum analysis every 12 months ± 6 months as outlined below. Patients can schedule the blood draw at their convenience, or this may be combined with a routine doctor's appointment. There are no study-mandated interventions or assessments planned. Clinical data will

be accrued over 5 years during routine clinical encounters. At month 60, participation in the study will be terminated. Patients who at any point sign a consent for an outside clinical trial or other registry will be flagged and will temporarily discontinue participation in TARGET-PBC.

OPTIONAL PRO SURVEYS

Patients enrolled in TARGET-PBC are invited to complete PRO surveys every 6 months by phone or a web-based system. These surveys are optional and participation in this component does not affect participation in the main study. The PROs include the PBC-40,[12] 5-D pruritis scale (5-D itch),[13] and the Patient Reported Outcome Measurement Information System Fatigue–Short Form 8a.[14] Additional PROs may be added throughout the course of the study. Any additional PROs will be approved by the IRB prior to participant completion.

OPTIONAL BIOREPOSITORY SAMPLES

Blood samples for biomarker and DNA/RNA assays and serum analysis are collected on a voluntary basis, and participation in this component of the study does not affect participation in the main study. These samples are shipped to a central repository for storage to use in future analyses and studies as detailed below. In order to begin participation in the Biorepository Specimen Bank, patients must provide an additional consent. Obtaining samples for biomarkers or DNA/RNA at a given site will be contingent on that site's

TABLE 4. TABLE OF PROCEDURES FOR TARGET-PBC

Activity	Screening/ Enrollment Visit*	Follow-Up									
		Year 1		Year 2		Year 3		Year 4		Year 5	
Month	0§	3, 6, 9	12	18	24	30	36	42	48	54	60
Informed consent	X										
Inclusion/exclusion	X										
Blood sample collection†	X		X		X		X		X		X
Patient reported outcome surveys‡	X	X‡	X	X	X	X	X	X	X	X	X
Medical records submission‖	X§	X	X	X	X	X	X	X	X	X	X

*Study procedures are completed at a regularly scheduled clinic visit.
†Participants will be asked to provide an optional annual blood sample. Blood will be collected during a regular clinic visit approximately 12 months but not more than 18 months from the previous collection.
‡Participants will be asked to complete optional, web-based patient reported outcome surveys approximately every 6 months.
‖3 years of redacted historical records (Month 0) will be submitted following the Screening/Enrollment visit.
§During the follow up period, redacted medical records will be submitted every 3 months during year 1 and every 6 months during years 2-5. The first submission during the follow-up period will be 3 months following the Screening/Enrollment visit. Additional interim medical records submissions may be requested.

IRB regulations. Collected samples will be stored indefinitely. These samples can be used for research and teaching purposes or for research toward the development of new medical products or diagnostic tests relevant to PBC. Patients receive a small monetary incentive if they choose to participate in this portion of the study.

DATA MANAGEMENT

All data are collected, processed, transmitted, and stored by an electronic data capture system. TARGET PharmaSolutions abstractors are personally trained by the TARGET-PBC Steering Committee Chair; they review and abstract entered data. Later, clinical monitors review and ensure that these data correspond with data in the source documents (i.e., redacted medical records). Data management activities, such as query management and coding of adverse event terms, are performed by TARGET PharmaSolutions or its designee. Both abstractors and monitors are well trained and can email the Chair or members of the Steering Committee with specific questions at any time. This system of multiple levels of data control promotes transparency and accuracy.

Specific efforts are made to investigate and document the reasons for missing data, including lost-to-follow-up data. The appropriate analysis strategy for managing incomplete data depends on the nature of the particular analysis of interest and on the nature of the underlying mechanisms responsible for the occurrence of missing values. In some cases, the pattern of missing values is itself of interest; in other cases, established likelihood-maximization methods, analogous to those used in human immunodeficiency virus observational studies,[15] are used to manage missing data mechanisms that are noninformative and can be legitimately ignored.

PLANS FOR STATISTICAL ANALYSIS

This longitudinal observational study will use analytical methods to characterize primary and secondary aims. Outcomes of interest based on the research aims will be collected for each participant. Baseline characteristics of each participant will be collected to provide covariate-adjusted proportions, means, and rates (as needed), with corresponding measures of variability. Longitudinal analyses of the experiences of the participants will involve event incidence rates, risk factors, adverse events, and relative risk-type estimates. There will be estimates to investigate and document any incomplete data. Auxiliary analyses will be conducted to guide levels of confidence in the main results.

Discussion

TARGET-PBC is a longitudinal observational study conducted in both academic and community sites to create a real-world view of the natural history and clinical management of PBC in patients who are diagnosed and treated in this setting. Importantly, data generated from this study will address gaps in our knowledge of the clinical effectiveness of PBC-related interventions and provide valuable postmarketing surveillance of new PBC therapies. Special populations that might be excluded or underrepresented in clinical trials will be represented in this study, including ethnic minorities, patients with advanced cirrhosis, and those with an overlap syndrome with autoimmune hepatitis. Furthermore, most natural history data are limited to tertiary centers or large administrative database studies; TARGET-PBC allows a broader inclusion of patients being managed for PBC rather than those assumed to have PBC through administrative billing codes.

With this setup, TARGET-PBC seeks to understand the natural history of PBC and to describe PBC management techniques as they exist in a real-world setting. As regulatory authorities, such as the FDA, approve new medications, this data set can serve to monitor for drug-related adverse events and the impact of new interventions on liver, autoimmune, and neoplastic outcomes. TARGET-PBC is based on the model used for hepatitis C virus (HCV)-TARGET, a cooperative academic consortium that guides safe and effective use of direct-acting antivirals approved for the treatment of chronic HCV infection and which has been extremely successful providing real-world safety and effectiveness data for newer therapies.[16] While there are only two drugs currently approved for PBC (UDCA and OCA), several other promising therapies are currently under investigation, and TARGET-PBC will capture these new therapies as they enter the market.

Given the very long clinical course of PBC, clinical trials are often unable to ascertain hard endpoints, such as clinical decompensation, need for liver transplant, or death, and instead assess efficacy through impact on surrogate endpoints. That was the case for OCA, which was granted accelerated approval by the FDA

based on improvement in serum ALP. For this reason, continued approval of OCA is dependent on confirmation of the beneficial effects in subsequent studies evaluating its efficacy in improving clinically relevant endpoints.[10] Therefore, a phase 3b study of OCA evaluating clinical outcomes in patients with primary biliary cholangitis (COBALT) is in progress and is expecting to enroll 350 patients and have follow-up for approximately 8 years to answer this question. TARGET-PBC is designed to assess similar endpoints in a large population of patients with PBC in real life, which will complement this ongoing study. Furthermore, beyond measuring clinical effectiveness, postmarketing, real-world, rigorous, observational studies are important for collecting and interpreting PROs.[17] In addition, TARGET-PBC encourages interactions between all stakeholders, including the investigators, patient representatives, industry partners, and regulatory authorities. Any stakeholder may submit a scientific query to the steering committee, and this will trigger proper database analyses and data generation, thus promoting scientific output and perhaps accelerating postmarketing safety and efficacy evaluations.

As with other methodology papers, the benefits of this one are to promote prospective registration, increase collaboration, decrease duplication of research efforts, boost recruitment and referrals, and allow for published medical searches and systematic reviews to identify all relevant work. The TARGET-PBC study has prespecified hypotheses to decrease bias and promote transparency and accuracy in research.

In summary, TARGET-PBC is using standardized data collection practices, study data monitoring, and a comprehensive observational protocol to increase the efficiency of performing clinical research while ensuring collection of detailed critical safety and effectiveness data on prescribed PBC therapies. TARGET-PBC engages community and academic practice providers as partners in the research to ensure rapid translation of research findings into improvement in health care quality and outcomes. Furthermore, the availability of an established cohesive research network allows nimble responses to investigations of new treatment paradigms with existing agents as well as future generations of PBC therapies.

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