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CLINICAL—BILIARY

Levels of Alkaline Phosphatase and Bilirubin Are Surrogate End Points of Outcomes of Patients With Primary Biliary Cirrhosis: An International Follow-up Study

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This article has an accompanying continuing medical education activity on page e15. Learning Objective: Upon completion of this CME exam, successful learners will understand the concept and importance of surrogate end points in medicine and be aware of the proposed four-level hierarchy of evidence for validation. Further, they will be able to apply this knowledge to a particular disease, namely primary biliary cirrhosis.

See Covering the Cover synopsis on page 1194.

BACKGROUND & AIMS: Noninvasive surrogate end points of long-term outcomes of patients with primary biliary cirrhosis (PBC) are needed to monitor disease progression and evaluate potential treatments. We performed a meta-analysis of individual patient data from cohort studies to evaluate whether patients' levels of alkaline phosphatase and bilirubin correlate with their outcomes and can be used as surrogate end points. **METHODS:** We performed a meta-analysis of data from 4845 patients included in 15 North American and European long-term follow-up cohort studies. Levels of alkaline phosphatase and bilirubin were analyzed in different settings and subpopulations at different time points relative to the clinical end point (liver transplantation or death). **RESULTS:** Of the 4845 patients, 1118 reached a clinical end point. The median follow-up period was 7.3 years; 77% survived for 10 years after study enrollment. Levels of alkaline phosphatase and bilirubin measured at study enrollment (baseline) and each year for 5 years were strongly associated with clinical outcomes (lower levels were associated with longer transplant-free survival). At 1 year after study enrollment, levels of alkaline phosphatase that were 2.0 times the upper limit of normal (ULN) best predicted patient outcome (C statistic, 0.71) but not significantly better than other thresholds. Of patients with alkaline phosphatase levels $\leq$2.0 times the ULN, 84% survived for 10 years compared with 62% of those with levels >2.0 times the ULN ($P < .0001$). Absolute levels of alkaline phosphatase 1 year after study enrollment predicted patient outcomes better than percentage change in level. One year after study enrollment, a bilirubin level 1.0 times the ULN best predicted patient transplant-free survival (C statistic, 0.79). Of patients with bilirubin levels $\leq$1.0 times the ULN, 86% survived for 10 years after study enrollment compared with 41% of those with levels >1.0 times the ULN ($P < .0001$). Combining levels of alkaline phosphatase and bilirubin increased the ability to predict patient survival times. We confirmed the predictive value of alkaline phosphatase and

†Deceased.

Abbreviations used in this paper: CI, confidence interval; HR, hazard ratio; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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bilirubin levels in multiple subgroups, such as patients who had not received treatment with ursodeoxycholic acid, and at different time points after study enrollment. **CONCLUSIONS:** Levels of alkaline phosphatase and bilirubin can predict outcomes (liver transplantation or death) of patients with PBC and might be used as surrogate end points in therapy trials.

Keywords: Autoimmune Liver Disease; Response To Treatment; Biomarker; New Therapies.

Primary biliary cirrhosis (PBC) is a rare, chronic, and slowly progressive autoimmune hepatobiliary disease. PBC typically progresses to cirrhosis, which may lead to complications from liver failure and premature death.[1] Presently, most patients with PBC are treated with ursodeoxycholic acid (UDCA), the only approved therapy for PBC, which is in keeping with treatment guidelines.[2,3] Although UDCA therapy has a marked impact on clinical outcomes in patients with PBC, up to 40% of patients have an insufficient response to this treatment and accordingly have a significantly increased risk of developing an adverse outcome, such as liver transplantation or death.[4–8] Therefore, there is a pressing unmet medical need for better therapies for this serious disease.

A major challenge for patients, health care providers, and drug developers is the slowly progressive nature of PBC, which effectively precludes the evaluation of classic clinical outcomes such as transplant-free survival. The low prevalence of PBC also represents a significant barrier to conducting large controlled clinical outcome trials in patients with this disease. Clinical end points such as liver transplantation and death were evaluated in an early primary interventional trial of UDCA in patients with PBC,[9] but most cases of PBC are now diagnosed at an earlier stage of disease and UDCA therapy is initiated shortly after diagnosis, further affecting the ability to assess the clinical benefit of new PBC therapies in a timely and realistic manner. Thus, the evaluation of scientifically valid surrogate parameters for clinical outcomes is inevitable at least at some stage in the development pathway. Further evaluation of possible surrogates for clinical benefit are needed, particularly with a focus on using large data sets that are representative of the spectrum of disease globally and sufficiently powered through size, duration of follow-up, and numbers of clinical events to refine the scientific validity of specific biochemical surrogates.

Serum bilirubin is well established as an independent predictor of prognosis in PBC, regardless of treatment.[10–12] In addition, bilirubin has previously been shown to be predictive of clinical outcomes across other liver diseases and is incorporated in several commonly used prognostic scoring models, such as the Child–Turcotte–Pugh score,[13,14] the Model of End-Stage Liver Disease (MELD),[15] and, specifically in PBC, the Mayo PBC score.[16] However, despite the proven prognostic value of bilirubin, only patients with relatively advanced disease are likely to show meaningful changes in bilirubin levels that are stratifying. A biochemical variable and potentially more broadly applicable surrogate end point is alkaline phosphatase, an isoenzyme involved in dephosphorylation.[17] An elevated level of alkaline phosphatase, a marker of cholestasis, is typically seen across the spectrum of PBC disease severity and is a key component of the diagnosis of PBC in both the American and European guidelines.[2,3] The relationship between alkaline phosphatase levels and the risk of adverse outcomes in PBC has been extensively documented in several relatively small studies,[4,5,7,8,18,19] but no systematic effort has been reported to date using a pooled meta-analysis approach to validate a biochemical surrogate for use in clinical studies of PBC.

We sought to investigate how serum alkaline phosphatase and bilirubin levels individually and in combination, correlate with transplant-free survival to determine the prognostic significance of these biochemical variables and hence their utility as robust surrogate end points for therapeutic PBC trials. To do so, we assembled a large, international, observational PBC database, allowing for a robust individual patient–level meta-analysis, to ensure both a rigorous statistical assessment and widespread applicability.

Patients and Methods

Study Design and Study Population

This study was a meta-analysis performed by the Global PBC Study Group, an international and multicenter collaboration between 15 liver centers in 8 North American and European countries, which combined individual patient data from major long-term follow-up cohorts. Most individual databases contained prospectively collected follow-up data on patients starting UDCA therapy.

This study was conducted in accordance with the protocol and the principles of the Declaration of Helsinki. The protocol was reviewed and approved by the institutional research board of the corresponding center and at each participating center in accordance with local regulations.

Both UDCA-treated and nontreated patients with an established diagnosis of PBC in accordance with European and American guidelines were eligible for inclusion in this study.[2,3] Patients were excluded from analysis if follow-up data were insufficient or unavailable, the start date of treatment or the exact date of major clinical events was unknown, or they had concomitant liver disease.

Data Collection and Quality Assessment

Collected clinical and laboratory data included sex, age, diagnosis of PBC, liver histology, treatment (type of medication, dosage, and duration), duration and last date of follow-up, baseline antimitochondrial antibody status, baseline and yearly laboratory levels (serum alkaline phosphatase, total bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, and platelets), and outcomes (death and cause of death, liver transplantation, hepatocellular carcinoma, ascites, and variceal bleeding).

Liver histology performed within 1 year of study entry or documented cirrhosis before study entry was classified as a baseline biopsy. Histological data was assessed for severity according to Ludwig[20] and Scheuer's[21] classification. Disease stage was classified histologically as early (stage I and II) or late

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