Obeticholic acid is associated with improvements in AST-to-platelet ratio index and GLOBE score in patients with primary biliary cholangitis

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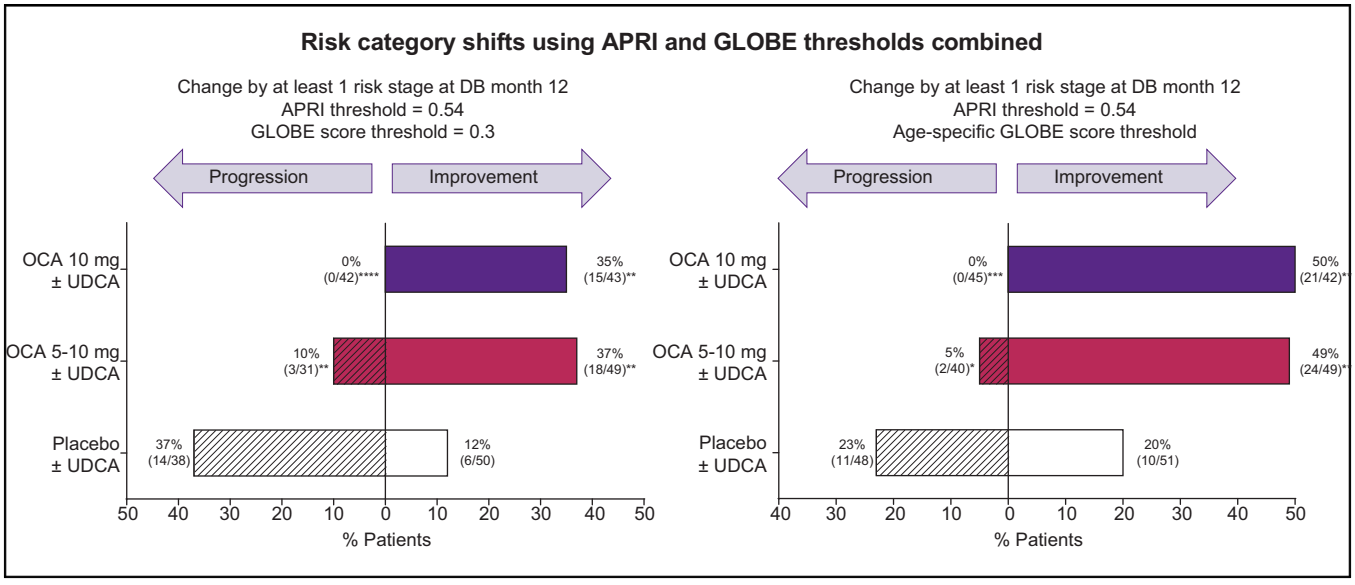
Graphical abstract



Highlights

- Biochemical markers can help estimate risk of progression in patients with primary biliary cholangitis.
- Data from the POISE trial were used to calculate GLOBE score and aminotransferase-to-platelet ratio index.
- Obeticholic acid treatment was associated with a shift to lower risk of progression.

Lay summary

Primary biliary cholangitis (PBC) is a chronic disease affecting the liver. People who suffer from PBC are at risk of serious long-term complications. Information from certain blood tests can be used to estimate the likelihood of experiencing long-term complications. The results of this study showed that based on blood test results, people taking obeticholic acid, with or without ursodeoxycholic acid, for PBC were predicted to have a better outcome than those taking placebo.

https://doi.org/10.1016/j.jhepr.2020.100191

Research article

JHEP|Reports

Obeticholic acid is associated with improvements in AST-to-platelet ratio index and GLOBE score in patients with primary biliary cholangitis☆

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JHEP Reports **2021.** https://doi.org/10.1016/j.jhepr.2020.100191

Background & Aims: Biochemical markers, including GLOBE score and aspartate aminotransferase-to-platelet ratio index (APRI), are used to stratify risk in patients with primary biliary cholangitis (PBC). This study aimed to evaluate the effects of obeticholic acid (OCA) on categorical shifts in GLOBE score, APRI, and both combined, based on data from POISE, a phase III placebo-controlled trial in patients with PBC who had an incomplete response or were intolerant to ursodeoxycholic acid.
Methods: In a *post hoc* analysis, baseline and Month 12 data from POISE were used to calculate the APRI and GLOBE score. Patients were stratified into 3 risk groups based on a combination of APRI (0.54) and GLOBE (0.3 or age-specific) thresholds.
Results: The analysis included 215 patients (47 low risk; 79 moderate risk; 89 high risk). Using the combined GLOBE score (threshold of 0.3) and APRI thresholds, there was improvement in ≥1 risk stage in 37% and 35% of patients in the OCA 5–10 mg and 10 mg groups, respectively, *vs.* 12% in the placebo group (both p <0.05). Progression occurred in 10% and 0% in the 5–10 mg and 10 mg groups *vs.* 37% in the placebo group. Results with GLOBE age-specific thresholds were similar.
Conclusions: Based on change in APRI and GLOBE score at 12 months, OCA treatment is associated with reduction in the predicted risk of liver-related complications in patients with PBC.
Clinical trials registration: NCT01473524.

Introduction

Primary biliary cholangitis (PBC) is characterised by the destruction of intrahepatic bile ducts, cholestasis, and progressive inflammation that leads to fibrosis and the subsequent development of cirrhosis and its potentially fatal complications.[1,2] Cirrhosis-related complications in patients with PBC include ascites, variceal bleeding, hepatic encephalopathy, and other complications related to hepatic decompensation.[3] These complications predict the need for liver transplantation and increased risk of death.[3,4] Previously, ursodeoxycholic acid (UDCA) was the only approved treatment for PBC, and remains the standard first-line therapy associated with reduced mortality.[1,2,5] However, UDCA does not prevent progression to cirrhosis and liver failure in all patients, and those with an incomplete biochemical response to UDCA are most at risk of an unfavourable outcome.[6] Obeticholic acid (OCA) is a highly selective and potent farnesoid X receptor (FXR) agonist that activates FXR, a key regulator of inflammation, and bile acid homeostasis.[7] Compared with placebo, OCA treatment was associated with significant improvement in liver chemistry in patients with PBC and an inadequate response to UDCA.[8]

Biochemical markers have proven useful for risk stratification in PBC.[6,9–12] Two strategies that combine biochemical markers to evaluate risk are aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and the GLOBE score developed and validated by the Global PBC Study Group.[6,12] Developed as a marker of cirrhosis and portal hypertension in patients with hepatitis C, APRI has been shown to predict risk in PBC regardless of response to UDCA.[12,13] Analyses based on a cohort of PBC patients determined that an APRI above a threshold of 0.54 is associated with poorer clinical outcomes.[12] In the phase III POISE trial investigating OCA in patients with PBC, OCA was associated with a significant decrease in AST compared with placebo at the end of the 12-month double-blind treatment period.[8] The GLOBE score is a prognostic algorithm to predict liver transplant (LT)-free survival in PBC patients treated with UDCA.[6] The GLOBE score can be evaluated using an overall threshold (0.3) or age-specific threshold, which separates patients into 5 age groups and matches them with an age- and sex-matched population.[6]

Keywords: APRI; Cholestasis; PBC; Risk stratification.
Received 25 March 2020; received in revised form 12 August 2020; accepted 5 September 2020; available online 29 September 2020
☆Previous publication: Hirschfield G, *et al.* Presented at AASLD 67th Annual Meeting; 2016; Boston, MA (Oral 209). Harms M, *et al.* Presented at EASL 52nd International Congress; 2017; Amsterdam, The Netherlands (Poster 527).
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A GLOBE score below threshold is associated with a LT-free survival similar to that of a matched normal population, whereas a GLOBE score above threshold is associated with significantly diminished LT-free survival.[6] Following 12 months of OCA treatment, calculation of the GLOBE score using data from the POISE trial indicated a significant reduction in the risk of death or liver transplantation at 5, 10, and 15 years.[14] The combination of both APRI threshold and GLOBE score threshold has demonstrated the ability to stratify patients more accurately than either score alone for predicting the risk of major liver-related complications.[3]

The aim of the current study was to evaluate the biochemical response to OCA treatment through categorical shifts in APRI and/or GLOBE score in patients with PBC, based on data from the POISE trial.[8]

Patients and methods

Study design and treatment

POISE (NCT01473524) was a randomised, double-blind, placebo-controlled, pivotal phase III trial evaluating the efficacy, safety, and tolerability of OCA 5 to 10 mg daily in addition to UDCA in patients with PBC who had incomplete response to UDCA or as a monotherapy in patients who were intolerant to UDCA.[8] Randomisation was stratified based on Paris 1 risk criteria (alkaline phosphatase [ALP] >3 × the upper limit of normal [ULN] and/or AST >2 × ULN and/or bilirubin >ULN) and the use of UDCA.[8] In this *post hoc* analysis, APRI and GLOBE score were calculated using laboratory indices (AST, ALP, bilirubin, albumin, and platelet count) collected at baseline, scheduled study visits, and at the end of the double-blind phase (Month 12).

APRI

The APRI was calculated according to the formula of Wai *et al.*:[9]

$$\text{APRI} = \text{AST level/ULN/platelet count } (10^9/\text{L}) \times 100.$$

GLOBE score

Baseline and Month 12 data from POISE were entered into the GLOBE score algorithm, where LN represents the natural logarithm:[6]

$$0.044378 \times \text{age at start of UDCA therapy} + 0.93982 \times \text{LN (bilirubin times the ULN at 1-year follow-up)} + 0.335648 \times \text{LN (ALP times the ULN at 1-year follow-up)} - 2.266708 \times \text{albumin levels} \times \text{the lower limit of normal [LLN] at 1-year follow-up} - 0.002581 \times \text{platelet count per } 10^9/\text{L at 1-year follow-up} + 1.216865$$

For baseline characteristics and safety assessments, all patients who had baseline parameters for GLOBE score evaluations were included. For assessing categorical shifts in GLOBE score, only patients with both baseline and Month 12 GLOBE scores available were evaluated. Patients were assessed by the overall threshold (0.3) and by age-specific thresholds developed by the Global PBC Study Group. The age-specific thresholds were defined as follows: −0.52 for <45 years, 0.01 for ≥45 to <52 years, 0.60 for ≥52 to <58 years, 1.01 for ≥58 to <66 years, and 1.69 for ≥66 years.[6] A score below the age-specific threshold was associated with a prognosis similar to that of a matched normal population.

Table 1. Risk group categories based on APRI and GLOBE score.

Risk group	Definition
Low-risk group	APRI ≤0.54 AND GLOBE score ≤threshold*
Moderate-risk group	APRI ≤0.54 AND GLOBE score >threshold*, OR APRI >0.54 AND GLOBE score ≤threshold*
High-risk group	APRI >0.54 AND GLOBE score >threshold*

APRI, aspartate aminotransferase-to-platelet ratio index.
*Analyses based on the overall threshold used 0.3 as the threshold value, whereas analyses using age-specific thresholds used −0.52 for <45 years, 0.01 for ≥45 to <52 years, 0.60 for ≥52 to <58 years, 1.01 for ≥58 to <66 years, and 1.69 for ≥66 years.[6]

Risk group stratification

Patients were pooled by risk groups, which were determined using both the overall and the age-specific thresholds for the various analyses: the low-risk group was defined as APRI ≤0.54 and GLOBE score ≤ threshold; the moderate-risk group was defined as APRI ≤0.54 and GLOBE score > threshold, or APRI >0.54 and GLOBE score ≤ threshold; and the high-risk group was defined as APRI >0.54 and GLOBE score > threshold.

Analyses

Patients in each risk group were assessed for categorical shifts in APRI and/or GLOBE score at Month 12 compared with baseline (Table 1). For the analyses of categorical shifts in APRI and/or GLOBE scores, patients without paired observations were excluded. In addition, patients in the low-risk group were excluded from the improvement analysis as they were incapable of further categorical improvement; similarly, patients from the high-risk group were incapable of further categorical worsening and therefore were not included in the progression analysis. Analyses of progression and improvement were completed using a Cochran-Mantel-Haenszel test stratified by randomisation stratification factors. Statistical testing was 2-sided and performed at the 0.05 alpha level. Odds ratios (ORs) and confidence intervals (CIs) comparing OCA groups with placebo were obtained using a logistic regression model with terms for treatment and randomisation stratification factors. The APRI was compared between OCA and placebo using an analysis of covariance model with changes from baseline as the dependent variable including treatment group and randomisation stratification factors as fixed effects and baseline as a covariate.

Results

Patient characteristics

This *post hoc* analysis included a total of 215 patients from the phase III POISE trial (Table 2). Overall, the number of patients in each risk group per the 0.3 GLOBE threshold/0.54 APRI threshold was small, with fewer patients in the low-risk group (n = 47) than in the moderate- (n = 79) or high-risk groups (n = 89). Within each risk group, the treatment groups were generally comparable in terms of demographics and disease characteristics at baseline likely owing to the randomisation stratification used in the POISE trial. The median values for baseline APRI ranged from 0.379 to 0.442 for the low-risk group, from 0.715 to 0.803 for the moderate-risk group, and from 1.096 to 1.287 for the high-risk group. The median values for baseline GLOBE scores

Table 2. Baseline demographics and disease characteristics by risk group.

Low-risk group (APRI ≤0.54, GLOBE score ≤0.3)	Placebo (n = 18)	OCA 5–10 mg titration (n = 11)	OCA 10 mg (n = 18)
Age, years; median (IQR)	50.5 (20.0)	55.0 (14.0)	52.5 (14.0)
Sex, n (%)			
Male	3 (17)	0	1 (6)
Female	15 (83)	11 (100)	17 (94)
Race, n (%)			
White	17 (94)	10 (91)	18 (100)
Black	0	0	0
Asian	0	0	0
Other	1 (6)	1 (9)	0
Duration of PBC, years; median (IQR)	7.1 (5.9)	9.9 (7.7)	5.0 (6.2)
UDCA			
Current use, n (%)	18 (100)	11 (100)	18 (100)
Dose, mg/kg; median (IQR)	14.4 (3.8)	15.0 (3.6)	16.2 (6.6)
ALP, U/L; median (IQR)	273.28 (91.90)	250.35 (24.85)	249.94 (97.25)
Total bilirubin, mg/dl; median (IQR)	0.46 (0.22)	0.37 (0.14)	0.42 (0.22)
Direct bilirubin, mg/dl; median (IQR)	0.15 (0.09)	0.13 (0.04)	0.15 (0.10)
Albumin, g/L; median (IQR)	44.75 (3.00)	43.20 (3.00)	44.75 (2.00)
AST, U/L; median (IQR)	29.23 (9.33)	25.97 (7.95)	29.88 (6.20)
Platelets, $\times10^9$/L; median (IQR)	292.00 (66.50)	299.00 (67.50)	300.75 (88.00)
APRI; median (IQR)	0.442 (0.187)	0.379 (0.124)	0.420 (0.105)
GLOBE score; median (IQR)	−0.292 (0.783)	−0.248 (0.590)	−0.327 (0.731)
Moderate-risk group (APRI ≤0.54, GLOBE score >0.3 or APRI >0.54, GLOBE score ≤0.3)	**Placebo (n = 22)**	**OCA 5–10 mg titration (n = 26)**	**OCA 10 mg (n = 31)**
Age, years; median (IQR)	54.0 (11.0)	51.0 (8.0)	52.0 (12.0)
Sex, n (%)			
Male	0	1 (4)	3 (10)
Female	22 (100)	25 (96)	28 (90)
Race, n (%)			
White	21 (95)	25 (96)	31 (100)
Black	0	0	0
Asian	0	1 (4)	0
Other	1 (5)	0	0
Duration of PBC, years; median (IQR)	7.1 (9.1)	6.2 (5.7)	9.4 (7.7)
UDCA			
Current use, n (%)	21 (95)	25 (96)	29 (94)
Dose, mg/kg; median (IQR)	16.1 (3.3)	16.3 (5.9)	14.3 (5.4)
ALP, U/L; median (IQR)	315.2 (130.4)	256.0 (186.7)	287.8 (146.6)
Total bilirubin, mg/dl; median (IQR)	0.43 (0.21)	0.42 (0.24)	0.47 (0.26)
Direct bilirubin, mg/dl; median (IQR)	0.15 (0.11)	0.14 (0.14)	0.17 (0.12)
Albumin, g/L; median (IQR)	44.00 (2.65)	42.75 (3.15)	44.50 (3.70)
AST, U/L; median (IQR)	45.15 (20.80)	50.80 (22.25)	46.75 (25.65)
Platelets, $\times10^9$/L; median (IQR)	248.75 (57.00)	232.50 (62.50)	240.50 (83.00)
APRI; median (IQR)	0.715 (0.340)	0.803 (0.301)	0.727 (0.467)
GLOBE score; median (IQR)	−0.094 (0.324)	−0.240 (0.713)	0.009 (0.482)
High-risk group (APRI >0.54, GLOBE score >0.3)	**Placebo (n = 33)**	**OCA 5–10 mg titration (n = 33)**	**OCA 10 mg (n = 23)**
Age, years; median (IQR)	58.0 (14.0)	61.0 (11.0)	65.0 (13.0)
Sex, n (%)			
Male	2 (6)	4 (12)	5 (22)
Female	31 (94)	29 (88)	18 (78)
Race, n (%)			
White	28 (85)	32 (97)	21 (91)
Black	1 (3)	1 (3)	0
Asian	1 (3)	0	1 (4)
Other	3 (9)	0	1 (4)
Duration of PBC, years; median (IQR)	8.3 (10.0)	9.4 (10.3)	9.7 (11.5)
UDCA			
Current use, n (%)	29 (88)	29 (88)	19 (83)
Dose, mg/kg; median (IQR)	15.4 (5.1)	15.9 (5.0)	15.4 (4.1)
ALP, U/L; median (IQR)	316.30 (208.78)	339.55 (102.18)	311.33 (186.57)
Total bilirubin, mg/dl; median (IQR)	0.79 (0.47)	0.74 (0.38)	0.95 (0.59)
Direct bilirubin, mg/dl; median (IQR)	0.29 (0.49)	0.30 (0.29)	0.36 (0.40)
Albumin, g/L; median (IQR)	41.40 (3.50)	42.00 (4.00)	42.50 (5.60)
AST, U/L; median (IQR)	49.50 (31.85)	54.45 (32.35)	49.93 (50.00)
Platelets, $\times10^9$/L; median (IQR)	158.50 (116.00)	193.50 (119.00)	156.00 (63.00)
APRI; median (IQR)	1.178 (1.291)	1.096 (1.185)	1.287 (1.383)
GLOBE score; median (IQR)	1.257 (0.921)	0.727 (0.576)	1.207 (1.019)

ALP, alkaline phosphatase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; IQR, inter-quartile range; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

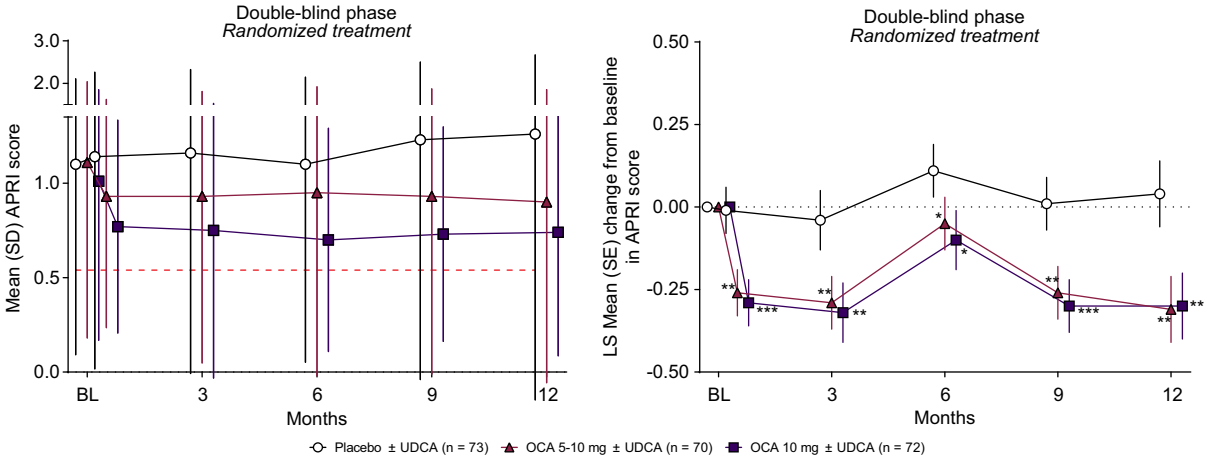

Fig. 1. Changes in APRI. Double-blind *p* value for comparing OCA with placebo was obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomisation strata factor. The dashed red line represents the APRI threshold of 0.54. **p* <0.05. ***p* <0.01. ****p* <0.0001. ANCOVA, analysis of covariance; APRI, aspartate aminotransferase-to-platelet ratio index; BL, baseline; LS, least square; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

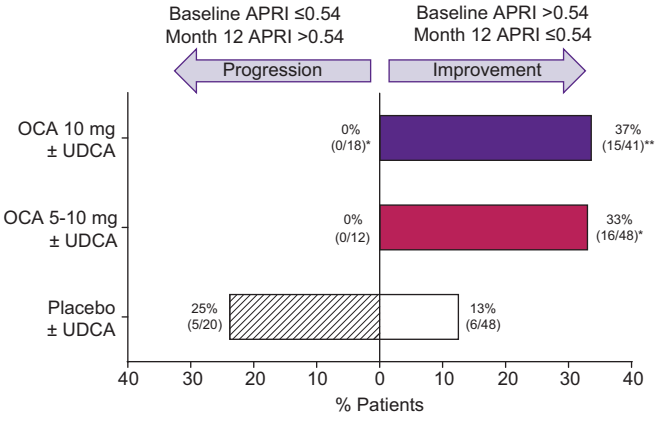

Fig. 2. Categorical changes in APRI after OCA treatment. Progression was defined as baseline APRI ≤0.54 and on treatment APRI >0.54; improvement was defined as baseline APRI >0.54 and on treatment APRI ≤0.54. Patients with evaluations at both baseline and double-blind Month 12 were included. *p* values were obtained using the Cochran-Mantel-Haenszel test. **p* <0.05. ***p* <0.01. APRI, aspartate aminotransferase-to-platelet ratio index; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

ranged from −0.327 to −0.248 for the low-risk group, from −0.240 to 0.009 for the moderate-risk group, and from 0.727 to 1.257 for the high-risk group. To perform shift analyses, both baseline and Month 12 values for APRI and GLOBE scores were available for 187 patients (87%).

Changes in APRI and GLOBE score

During double-blind treatment, both OCA groups had a significant decrease from baseline in APRI compared with placebo (*p* <0.01 at Month 12) (Fig. 1). No changes in platelet count were observed. Among patients with APRI ≥0.54 at baseline, 31 (35%) OCA-treated patients had APRI reduced to <0.54 by the end of the trial, *vs.* 6 (13%) placebo-treated patients (Fig. 2). Compared with placebo, the ORs (95% CIs) were 3.3 (1.1–9.7) for OCA 5–10 mg and 4.0 (1.3–11.8) for OCA 10 mg (Fig. S1).

Among patients with a GLOBE score ≥0.3 at baseline, OCA 5–10 mg *vs.* placebo treatment resulted in a greater percentage of patients achieving a GLOBE score ≤0.3 (27% *vs.* 6% for placebo; OR 5.5 [95% CI, 1.0–29.0], Fig. 3A and Fig. S1).Treatment with OCA 5–10 mg or OCA 10 mg resulted in fewer patients with a GLOBE score ≤0.3 at baseline progressing to a GLOBE score >0.3 (13% for 5–10 mg and 3% for 10 mg *vs.* 33% for placebo) (Fig. 3A). Results were consistent when using the age-specific thresholds, with 48% and 53% of patients achieving improvement with 5–10 mg (OR 3.7 [95% CI, 1.0–14.3]) and 10 mg OCA (OR 5.0 [95% CI, 1.2–21.8], Fig. 3B and Fig. S1), respectively, *vs.* 22% with placebo, and with 5% and 0%, respectively, progressing *vs.* 18% with placebo (Fig. 3B). Qualitatively, trends in categorical shifts in GLOBE score were consistent regardless of the threshold used (overall threshold of 0.3, and an age-specific threshold, Fig. 3B).

When patients were stratified into risk groups based on combined GLOBE and APRI criteria, with a GLOBE threshold of 0.3 and APRI threshold of 0.54, OCA treatment resulted in a greater percentage of patients improving by at least 1 risk stage (37%, OR 4.1 [95% CI, 1.5–11.7] with 5–10 mg and 35%, OR 3.9 [95% CI, 1.3–11.2] with 10 mg *vs.* 12% with placebo, Fig. 4A and Fig. S1) and a smaller percentage of patients progressing by at least 1 risk stage compared with placebo (10% with 5–10 mg and 0% with 10 mg *vs.* 37% with placebo, Fig. 4A). Results were similar when using the GLOBE age-specific thresholds: improvement occurred in 49% (OR 4.0 [95% CI, 1.6–9.7]) and 50% (OR 4.2 [95% CI, 1.7–10.5]) with 5–10 mg and 10 mg, respectively, *vs.* 20% with placebo, and progression in 5% and 0% with 5–10 mg and 10 mg *vs.* 23% with placebo (Fig. 4B and Fig. S1).

Safety

Detailed safety and tolerability data from the POISE trial have been previously reported.[8] In this *post hoc* analysis, the most common adverse event (AE) across all treatments and risk groups was pruritus; other common AEs were nasopharyngitis, headache, and fatigue (Table S1). These results are consistent with the AE data from the overall study.[8] The incidence of pruritus was higher in the OCA groups than in the placebo group for the moderate- and high-risk groups, but not for the low-risk group. There were no discontinuations in the low-risk group, 7

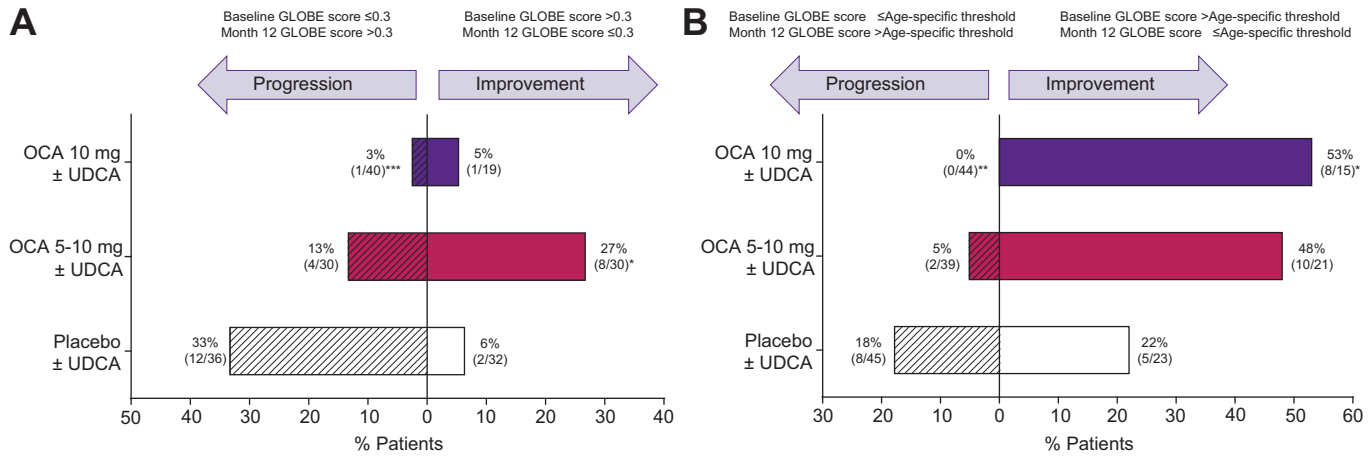

Fig. 3. Categorical changes in GLOBE score after OCA treatment. (A) GLOBE score by overall threshold (0.3). (B) GLOBE score by age-specific threshold. Age-specific threshold was defined as follows, for age based on consent date: −0.52 for <45 years; 0.01 for ≥45 to <52 years; 0.60 for ≥52 to <58 years; 1.01 for ≥58 to <66 years; 1.69 for ≥66 years. The *p* value was obtained using the Cochran-Mantel-Haenszel test. **p* <0.05. ***p* <0.01. ****p* <0.001. OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

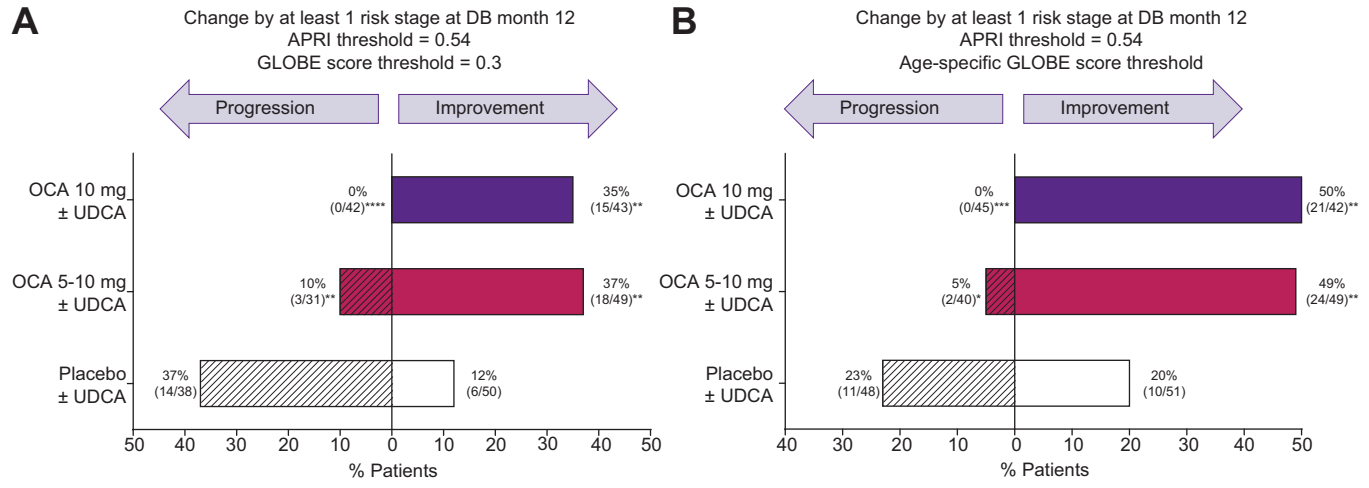

Fig. 4. Risk category shifts using APRI and GLOBE thresholds combined. (A) Risk category shifts using APRI and GLOBE (0.3) thresholds combined. (B) Risk category shifts using APRI and GLOBE (age-specific) thresholds combined. Progression was defined as a shift from a lower to higher risk category and improvement from a higher to lower risk category. Low risk: both scores ≤ threshold; moderate risk: one of the scores > threshold; high risk: both scores > threshold. *p* values were obtained using the Cochran-Mantel-Haenszel test. **p* <0.05. ***p* <0.01. ****p* <0.001. *****p* <0.0001. APRI, aspartate aminotransferase-to-platelet ratio index; DB, double-blind; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.

in the moderate-risk group (1 placebo; 2 OCA 5–10 mg; 4 OCA 10 mg), and 11 in the high-risk group (2 placebo; 4 OCA 5–10 mg; 5 OCA 10 mg). A total of 3 discontinuations in the moderate-risk group (1 OCA 5–10 mg; 2 OCA 10 mg) and 5 discontinuations in the high-risk group (all OCA 10 mg) were attributed to pruritus. Other AEs led to discontinuation in 1 patient in the moderate-risk group (OCA 10 mg) and 5 patients in the high-risk group (2 placebo; 3 OCA 5–10 mg).

Discussion

Regular evaluation of patient prognosis based on categorical shifts in APRI, GLOBE score, or a combination of both scores may aid in assessing response to therapy. In this study, treatment with OCA resulted in a significant improvement in APRI vs placebo. The decrease in APRI was consistent with the decrease in AST observed during the double-blind phase of the trial.[8] In the overall and age-specific GLOBE score thresholds, compared with placebo, OCA treatment resulted in fewer patients progressing to a GLOBE score associated with a higher risk of LT or death, and a greater percentage of patients achieving a GLOBE score associated with a prognosis similar to that of a normal population. Similar results were also observed with the APRI and GLOBE combined scores.

Of the patients treated with OCA 5–10 mg, none progressed in risk category by APRI score, whereas 87–97% of patients maintained their low-risk category without progression by overall and age-specific GLOBE and combined scores. Across all risk criteria assessed in this analysis, only a single patient receiving 10 mg OCA progressed in risk (using the GLOBE overall threshold). No patients receiving 10 mg OCA progressed using the combined risk criteria, age-specific GLOBE threshold, or APRI. The low percentage of patients receiving OCA 10 mg who shifted to the GLOBE score ≤0.3

category may have been as a result of high baseline GLOBE scores in this group compared with the other groups or a larger number of patients discontinuing from this group (9 *vs.* 6 in the OCA 5–10 mg group and 3 in the placebo group).

The relative number of LTs due to PBC appears to have decreased in the USA and Europe with the use of UDCA; however, in Europe, the absolute number of PBC-related LTs has remained stable over the past decade.[15,16] Approximately 40% of patients with PBC do not fully respond to UDCA and continue to require liver transplantation, indicating an unmet need for additional therapeutic options.[15,16] In the phase III POISE trial, OCA elicited significant improvements in markers of cholestasis and hepatocellular damage in patients with PBC who had an incomplete response to, or were intolerant of, UDCA.[8] Nevertheless, a partial response to UDCA is still associated with an improved hazard ratio compared with no treatment at all.[5] Although response criteria are important tools in evaluating new treatments and studies and are frequently negotiated with regulatory agencies, many diseases such as PBC exist on a continuous spectrum and are not fully quantified by dichotomous criteria.

This study adds to the growing body of literature on the use of scoring systems such as the GLOBE score to evaluate response to PBC treatment. The GLOBE score was originally developed to predict outcomes in patients treated with UDCA.[6] However, it is showing utility with other treatments as well.[14,17] A recent publication quantified the long-term benefit of OCA in the POISE trial through an analysis of data from POISE according to GLOBE score and also the United Kingdom-PBC (UK-PBC) score developed by the UK-PBC Consortium.[14] The GLOBE and UK-PBC scores were also used to assess the benefit of bezafibrate in combination with UDCA in a retrospective cohort of patients from the Japan PBC Study Group.[17] Both the GLOBE and UK-PBC scores include ALP and total bilirubin, which have been identified as the most important markers in determining LT-free survival in PBC.[18,19]

The approach of applying the combination of APRI and GLOBE to the POISE trial suggests that OCA has the potential to reduce long-term liver-related complications. However, the small sample size for each treatment group when stratified by risk was a limitation of this *post hoc* study. Long-term studies evaluating clinical outcome are required to confirm whether these results translate into overall clinical benefit, including a reduced risk of future hepatic complications, liver transplantation, and death. To this end, the ongoing phase IV COBALT trial (NCT02308111) is designed specifically to evaluate clinical outcomes in patients with PBC who are treated with OCA.[20] Data from COBALT could be used to validate the response to OCA as measured by combined criteria. In addition, longer-term data from the POISE trial will help to confirm the effect on clinical outcomes.

In conclusion, the results of this analysis based on biochemical markers further establish the utility of APRI and GLOBE score to assess the risk of liver-related complications in patients with PBC and support the use of OCA to reduce the risk of such complications, although confirmation of an effect on clinical outcomes is awaited.

Abbreviations

AE, adverse event; ALP, alkaline phosphatase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; DB, double-blind; FXR, farnesoid X receptor; IQR, inter-quartile range; LLN, lower limit of normal; LN, natural logarithm; LT, liver transplant; OCA, obeticholic acid; OR, odds ratio; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Financial support

The POISE trial, this *post hoc* analysis, and medical editorial assistance for this manuscript were supported by Intercept Pharmaceuticals, Inc.

Conflicts of interest

Maren H. Harms has received speaker fees from Zambon BV. Gideon M. Hirschfield has received consultancy fees from CymaBay, Gilead, GSK, Intercept, and Novartis, as well as grant funding from Gilead and Falk Pharma. Annarosa Floreani declares no conflicts of interest that pertain to this work. Marlyn J. Mayo has served on advisory committees or review panels for GSK, and has received grant/research support from Gilead, CymaBay, Intercept, Mallinckrodt, Novartis, Target, GSK, and Genfit. Albert Parés has received grant funding, personal fees, and advisory board fees from Intercept; personal fees and advisory board fee from Novartis; and personal fees from CymaBay and Inova Diagnostics. Alexander Liberman and Leigh MacConell are employees and shareholders of Intercept. Elizabeth Smoot Malecha is an employee of Intercept. Richard Pencek is a shareholder and former employee of Intercept. Bettina E. Hansen has received grant funding and personal fees from Intercept, CymaBay, and Albireo, and has received personal fees from Mirum and ChemoMab.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design as well as data acquisition M.H.H., G.M.H., A.F., M.J.M., A.P., B.E.H.

Data analysis: A.L, E.S.M., R.P., L.M.

Statistical analysis: E.S.M.

Access to the data, participation in drafting of the manuscript, reviewing the manuscript for intellectual content, approval of the final draft for submission: all authors.

Role of the funding source: the sponsor, Intercept Pharmaceutical Inc., participated in the study design, analysis and interpretation of data, in writing this report, and in the decision to submit the article for publication.

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

Acknowledgements

We thank Peggy Robinet, PhD, ProEd Communications, Inc., for her medical editorial assistance with this manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhepr.2020.100191.

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