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A SPECIAL MEETING REVIEW EDITION

Highlights in Primary Biliary Cholangitis From the EASL 2020 Digital International Liver Congress, the ACG 2020 Virtual Annual Scientific Meeting, and the AASLD 2020 Liver Meeting Digital Experience

Special Reporting on:

- Long-Term Efficacy and Safety of Obeticholic Acid in Patients With Primary Biliary Cholangitis: A Demographic Subgroup Analysis of 5-Year Results From the POISE Trial
- Long-Term Efficacy and Safety of Obeticholic Acid in Patients With Primary Biliary Cholangitis From the POISE Trial Grouped Biochemically by Risk of Disease Progression
- Long-Term Efficacy and Safety of Obeticholic Acid in Primary Biliary Cholangitis: Responder Analysis of More Than 5 Years of Treatment in the POISE Trial
- ENHANCE: Safety and Efficacy of Seladelpar in Patients With Primary Biliary Cholangitis—A Phase 3, International, Randomized, Placebo-Controlled Study
- Real-World Effectiveness of Obeticholic Acid in Patients With Primary Biliary Cholangitis
- Results of a Phase 2, Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of Saroglitazar Magnesium in Patients With Primary Biliary Cholangitis (EPICS)
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PLUS Meeting Abstract Summaries

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Long-Term Efficacy and Safety of Obeticholic Acid in Patients With Primary Biliary Cholangitis: A Demographic Subgroup Analysis of 5-Year Results From the POISE Trial

Primary biliary cholangitis (PBC) is a chronic autoimmune disease of the liver that damages the bile ducts, resulting in cholestasis and fibrosis if left untreated.[1,2] Patients are also at higher risk for hepatocellular carcinoma, osteoporosis, and osteopenia. The disease is rare and mainly diagnosed in women in their 40s. Importantly, the incidence appears to be steadily increasing in the United States, Europe, and Asia.[3-5] Ursodeoxycholic acid (UDCA), the standard first-line treatment, alters the course of the disease, but approximately 40% of patients do not benefit from this approach.[6,7]

Obeticholic acid (OCA) is a modified bile acid farnesoid X receptor agonist that was first approved by the US Food and Drug Administration (FDA) in May 2016 for use in conjunction with UDCA.[2] OCA acts on several steps in bile acid homeostasis, ultimately improving the clearance of bile acid from the body and decreasing the amount being made. It also reduces inflammation and cholestasis in the liver.[8] In addition, OCA is antifibrotic.

The phase 3 POISE trial evaluated OCA in patients with PBC. In the 12-month double-blind phase, patients were randomized to 1 of 3 arms: placebo with or without UDCA (73 patients), 5 mg of OCA with allowed adjustment to 10 mg with or without UDCA (70 patients), or 10 mg of OCA with or without UDCA (73 patients). Key inclusion criteria included a diagnosis of PBC; alkaline phosphatase (ALP) of at least 1.67 times the upper limit of normal (ULN) or total bilirubin greater than the ULN to less than 2 times the ULN; and inadequate response to UDCA or

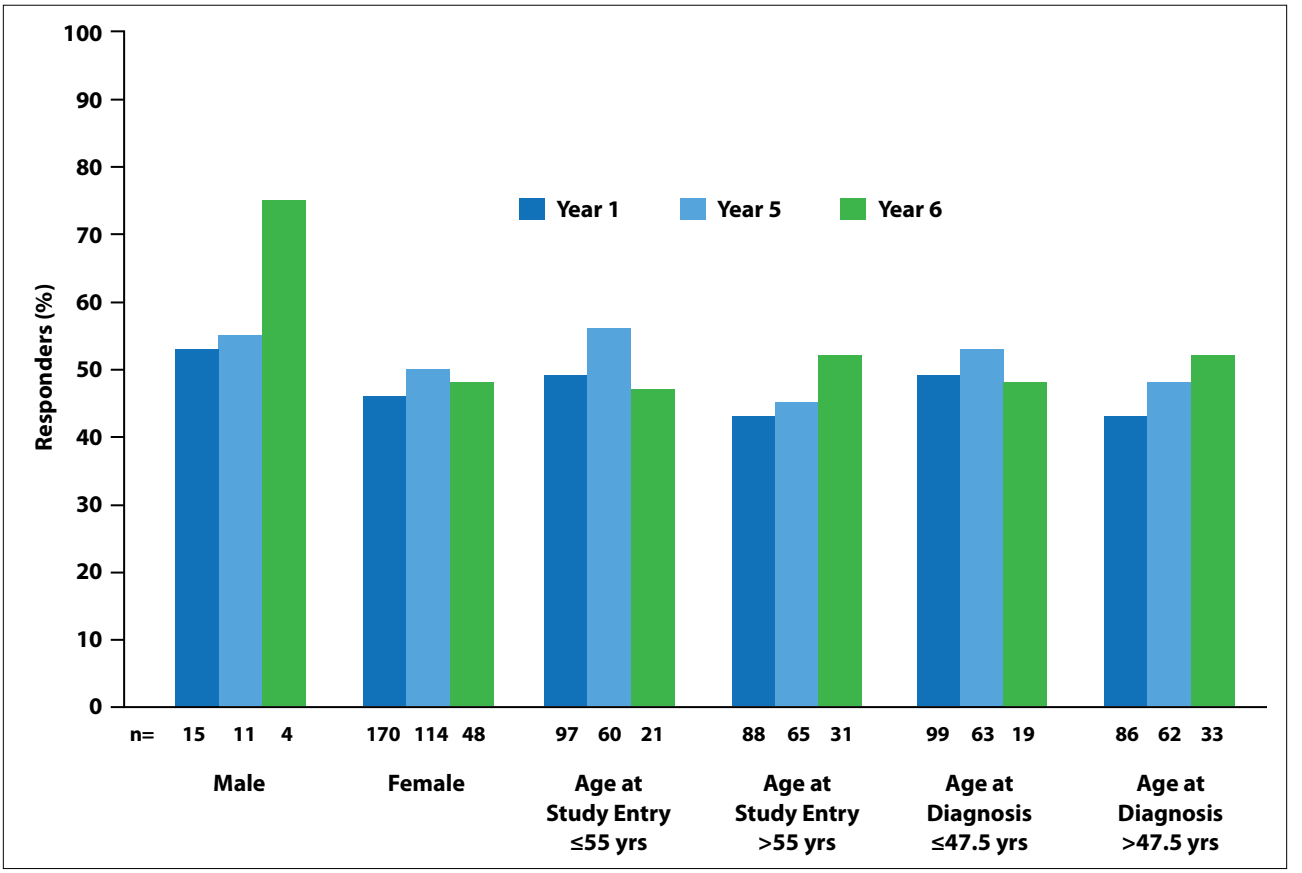

Figure 1. POISE primary endpoint (ALP <1.67 × ULN, total bilirubin ≤ ULN, and ALP reduction ≥15%) from OCA baseline by demographic subgroup. For patients who received placebo in the double-blind phase, OCA baseline was the last assessment prior to the first OCA dose in OLE. For patients who received OCA in the double-blind phase, OCA baseline was the mean of all available evaluations prior to double-blind treatment. ALP, alkaline phosphatase; OCA, obeticholic acid; OLE, open-label extension; ULN, upper limit of normal. Adapted from Bowlus CL et al. ACG abstract 58. Presented at the American College of Gastroenterology 2020 Virtual Annual Scientific Meeting; October 23-28, 2020.[10]

inability to tolerate it.[9] The primary POISE endpoint was ALP of less than 1.67 times the ULN, a reduction of at least 15% in ALP from baseline, and normal total bilirubin (≤ ULN) at 12 months.

The primary endpoint was met by 46% of patients in the 5-mg to 10-mg OCA arm and by 47% of patients in the 10-mg OCA arm, compared with 10% of patients in the placebo arm. In addition, PBC patients who received OCA for 12 months experienced significantly decreased levels of ALP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT), compared with those on placebo, as well as stabilization of total bilirubin.[9]

Following the 12-month double-blind phase of the POISE trial, patients were eligible to enter an open-label extension. All patients were treated with OCA 5 mg for 3 months, after which the dose could be titrated based on tolerability.

At the American College of Gastroenterology 2020 Virtual Annual Scientific Meeting, Dr Christopher L. Bowlus presented results from an analysis of the long-term efficacy and safety of OCA in demographic subgroups of patients who had been treated for 5 or more years in the POISE trial.[10] This analysis pooled double-blind placebo and double-blind OCA patients, and the demographic subgroups included age at study entry (≤55 years vs >55 years), age when diagnosed with PBC (≤47.5 years vs >47.5 years), and sex (male vs female).

A total of 193 of the 198 patients who completed the double-blind phase of the study enrolled in the open-label extension. Of these, 116 completed 5 years of OCA treatment, including 52 who received OCA in the double-blind phase and thus received a total of 6 years of OCA treatment. Figure 1 shows the POISE primary endpoint from OCA baseline by demographic subgroup for years 1, 5, and 6. Total bilirubin remained stabilized and the improvements in ALP were maintained across all subgroups after 6 years of treatment with OCA. Likewise, all of the subgroups sustained the improvements in both ALT and GGT that they achieved during the early phase of the study. In general, both ALT and AST were higher in the 2 younger-age subgroups. The most common side effect was mild to moderate pruritus, which occurred at similar rates in all demographic subgroups.

OCA led to sustained improvements in ALP, ALT, AST, and GGT as well as stabilization of total bilirubin through 5 years across demographic subgroups. Adverse events were consistent with OCA's established safety profile, and there were no new safety observations during long-term treatment. The researchers concluded that long-term OCA treatment is associated with durable improvements or stabilization in markers of disease severity in PBC patients, regardless of age or sex.

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Long-Term Efficacy and Safety of Obeticholic Acid in Patients With Primary Biliary Cholangitis From the POISE Trial Grouped Biochemically by Risk of Disease Progression

The risk posed by PBC can be gauged by measuring several biochemical markers, including ALP, ALT, AST, GGT, and bilirubin.[1] In particular, ALP and bilirubin are predictors of long-term outcomes among patients with PBC.[2] The results of the double-blind, phase 3 POISE study demonstrated that OCA reduced ALP, ALT, AST, and GGT and stabilized total bilirubin in patients with PBC.[3] Following this initial phase, the POISE trial continued with an open-label extension to assess the long-term safety and efficacy of OCA.

A poster presented at the American Association for the Study of Liver Diseases (AASLD) 2020 Liver Meeting Digital Experience examined long-term efficacy and safety of OCA according to subgroups defined by the risk of disease progression.[4] The researchers compared patients who had ALP of less than or equal to 3 times the ULN vs more than 3 times the ULN at baseline, and also compared patients who had total bilirubin of less than or equal to the ULN vs above the ULN at baseline.

In this analysis of the 193 patients who enrolled in the open-label extension, total bilirubin remained stable

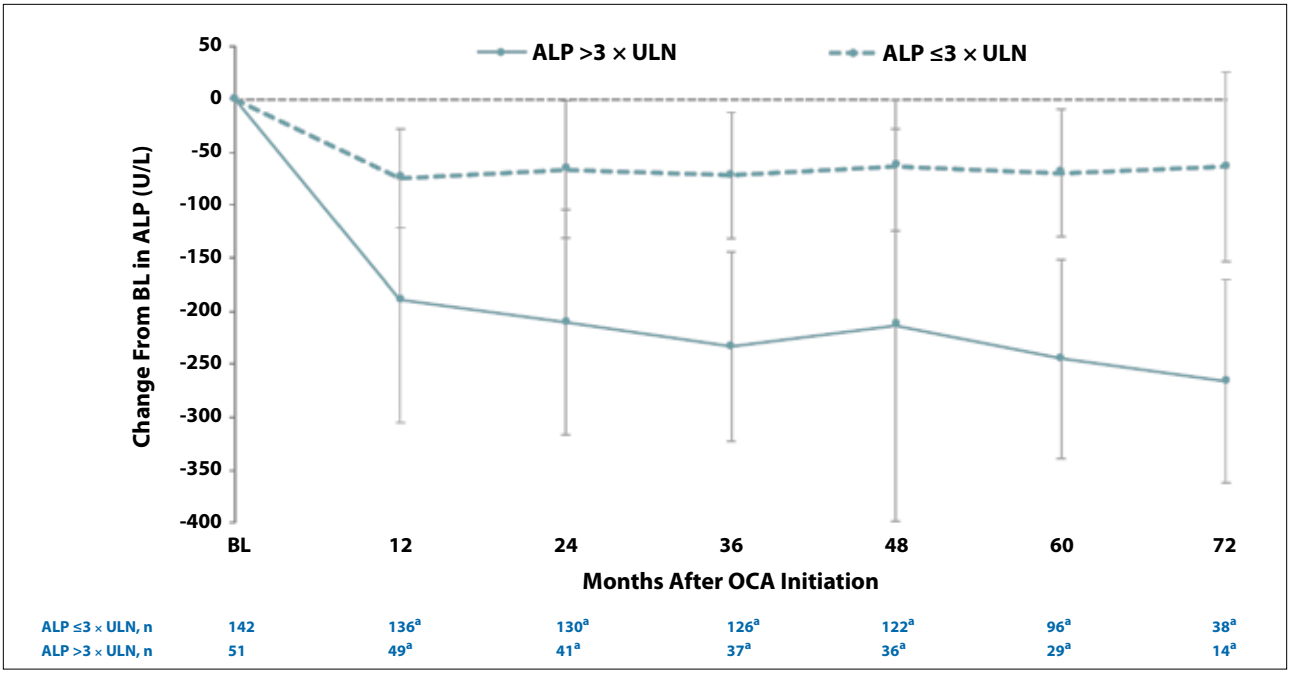

Figure 2. Mean (SD) change from BL in ALP levels through month 72 by biochemical subgroup. ALP, alkaline phosphatase; BL, baseline; OCA, obeticholic acid; SD, standard deviation; ULN, upper limit of normal. [a]*P*<.05 vs BL. Adapted from Bowlus CL et al. AASLD abstract 1250. *Hepatology*. 2020;72(suppl 1).[4]

among patients with bilirubin less than or equal to the ULN at baseline. After 72 months of treatment, patients who had ALP of greater than 3 times the ULN at baseline experienced a mean change in ALP of –266.3 U/L (Figure 2). Patients who had ALP of 3 times the ULN or less at baseline experienced a mean change of –63.9 U/L. For ALT, the mean change after 72 months of OCA treatment was –48.9 U/L among patients who had ALP above 3 times the ULN at baseline, and –20.9 U/L among patients who had ALP of 3 times the ULN or less at baseline. For AST, the respective mean changes were –27.3 U/L and –9.3 U/L.

Among the 142 patients whose ALP was 3 times the ULN or less at baseline, 8 (6%) reached a Model for End-Stage Liver Disease (MELD) score (an indicator of liver disease severity) of 15 or more after having a baseline MELD score of less than 12. By comparison, 5 of the 51 patients (10%) in the group with ALP above 3 times the ULN at baseline experienced this change in MELD score. Pruritus was the most common adverse event in all of the subgroups over 72 months of OCA treatment.

The researchers concluded that long-term OCA was effective and well tolerated, with lasting improvements in meaningful markers of liver injury and cholestasis, regardless of baseline ALP and total bilirubin.

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Long-Term Efficacy and Safety of Obeticholic Acid in Primary Biliary Cholangitis: Responder Analysis of More Than 5 Years of Treatment in the POISE Trial

The 12-month double-blind phase of the POISE trial had a primary endpoint of ALP of less than 1.67 times the ULN, a reduction of at least 15% in ALP from baseline, and total bilirubin of less than or equal to the ULN.[1] After this initial phase, PBC patients were able to enroll in a 5-year, open-label extension.

An analysis presented in a poster at the AASLD 2020 Liver Meeting Digital Experience assessed the safety and efficacy of OCA treatment over 5 years by comparing responders and incomplete responders.[2] The former were defined as patients who achieved the POISE primary endpoint after 1 year of OCA treatment and the latter

were defined as patients who did not.

The researchers found that 95 responders (48%) and 101 incomplete responders (52%) had ALP of less than 1.67 times the ULN, 179 responders (91%) and 18 incomplete responders (9%) had total bilirubin of less than or equal to the ULN, and 131 responders (67%) and 65 incomplete responders (33%) experienced a decrease in ALP of at least 15%.

The researchers analyzed changes from baseline in ALP, ALT, AST, GGT, and bilirubin (total and direct) for responders and incomplete responders. Figure 3 shows the mean change from baseline in ALP for responders and incomplete responders. The mean change from baseline at year 5 for responders and incomplete responders was –19 U/L and –28 U/L, respectively, for ALT; –9 U/L and –16 U/L, respectively, for AST; and 155 U/L and 165 U/L, respectively, for GGT. In addition, responders and incomplete responders experienced similar mean changes from baseline in direct bilirubin over the 72 months of the extension study. Pruritus was the most common adverse event among both responders and incomplete responders, but caused few patients to discontinue treatment.

The researchers concluded that OCA improved important biochemical markers of PBC, regardless of meeting the POISE primary endpoint, following 1 year of treatment with OCA. Changes in biochemical markers over time were frequently similar between groups, suggesting that the POISE primary endpoint does not completely capture the benefit of OCA.

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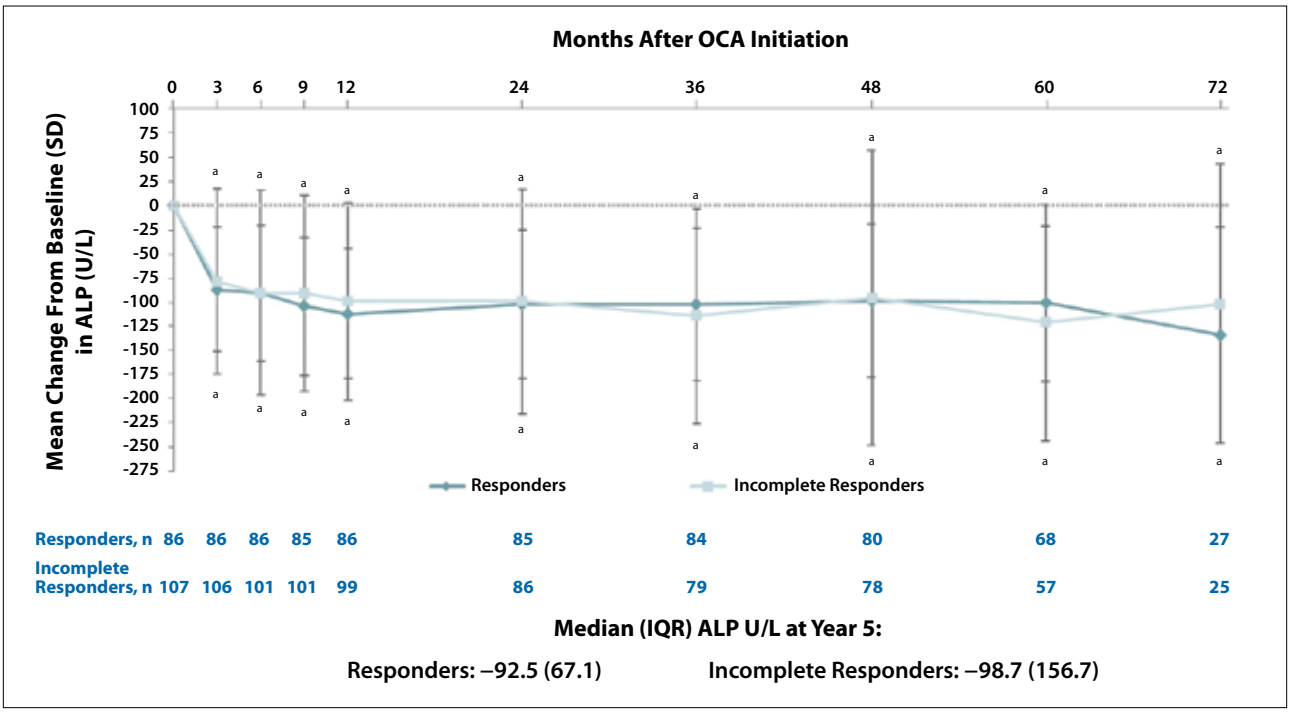

Figure 3. Mean (SD) change from baseline in ALP levels through month 72 by responder subgroup. [a]*P*<.05 vs baseline. ALP, alkaline phosphatase; IQR, interquartile range; OCA, obeticholic acid; SD, standard deviation. Adapted from Hansen BE et al. AASLD abstract 1251. *Hepatology*. 2020;72(suppl 1).[2]

ENHANCE: Safety and Efficacy of Seladelpar in Patients With Primary Biliary Cholangitis—A Phase 3, International, Randomized, Placebo-Controlled Study

Seladelpar is currently under investigation as a second-line treatment for PBC.[1] It is a potent and selective peroxisome proliferator-activated receptor (PPAR)-delta agonist, targeting a receptor found in hepatocytes, cholangiocytes, Kupffer cells, macrophages, and stellate cells—cell types that play a key role in liver disease. PPAR-delta agonism with seladelpar is both anti-inflammatory and antifibrotic. This approach also

reduces bile acids and increases lipid metabolism.

The phase 3 ENHANCE study investigated the use of seladelpar in patients with PBC who did not respond to first-line treatment, and findings were presented by Dr Gideon M. Hirschfield at the AASLD 2020 Liver Meeting Digital Experience.[2] Patients diagnosed with PBC were randomized to 1 of 3 treatment arms: seladelpar 10 mg (80 patients), seladelpar 5 mg for 26 weeks followed by an additional 26 weeks of either 5 mg or 10 mg (80 patients), or placebo (80 patients). The primary endpoint was a composite response by month 3 that included ALP of less than 1.67 times the ULN, a 15% or greater decrease in ALP, and total bilirubin at or below the ULN. The researchers also looked at whether ALP was normalized by month 3 and at the change from baseline in pruritus at month 3, and evaluated all of these measures at month 6.

An unexpected histologic finding in a clinical trial of seladelpar for nonalcoholic steatohepatitis led to early termination of the ENHANCE study. The finding turned out to be unrelated to the drug, but rather due to preexisting circumstance. The investigators conducted a blinded analysis following termination, as well as a safety analysis that included all patients who received at least 1 dose of seladelpar.

ABSTRACT SUMMARY Durability of Treatment Response After 1 Year of Therapy With Seladelpar in Patients With Primary Biliary Cholangitis: Final Results of an International Phase 2 Study

In this phase 2, open-label, uncontrolled, dose-finding study, 112 patients with PBC with an inadequate response to UDCA received seladelpar at a dose of 2 mg (11 patients), 5 mg (49 patients), or 10 mg (52 patients), with doses potentially increased up to 10 mg after 12 weeks, depending on biochemical response for 1 year (EASL abstract FRI133). Patients were mostly female and had an average age of 58 years. After a year of treatment, the mean decrease in ALP in the 5/10-mg group was 40%, and 45% in the 10-mg group. In the 5-mg group that escalated to 10 mg, 53% met the composite endpoint, as did 69% of patients who received 10 mg from the start.

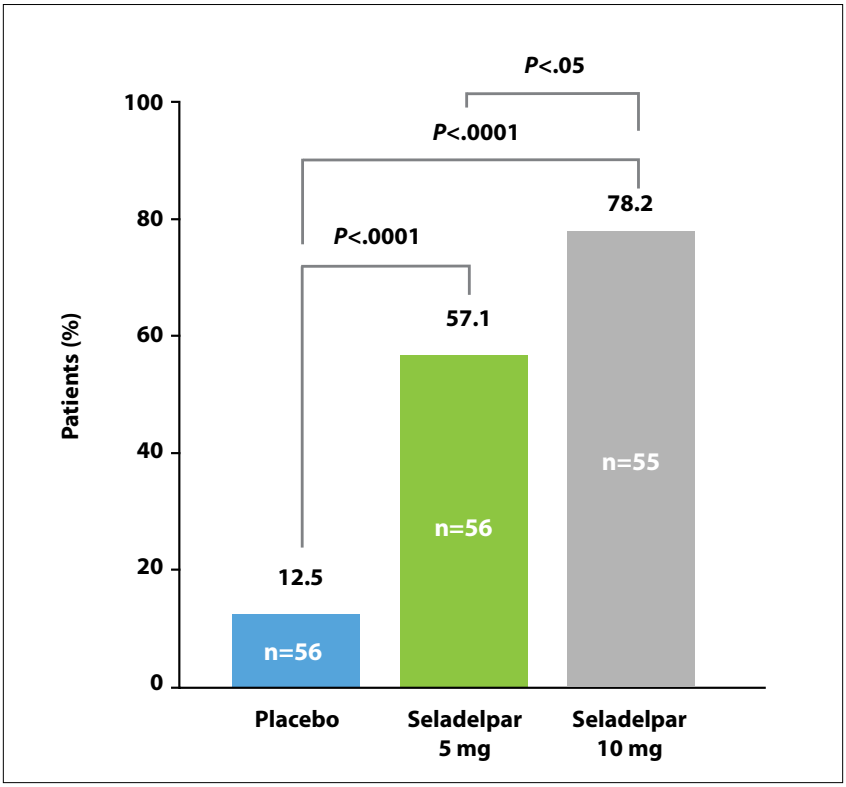

Figure 4. Primary composite endpoint achieved at 3 months with seladelpar. *P* values by Cochran-Mantel-Haenszel test. CymaBay, data on file 2020. Adapted from Hirschfield GM et al. AASLD abstract LO11. *Hepatology*. 2020;72(suppl 1).[2]

A composite response was achieved by 78.2% of patients in the 10-mg arm, 57.1% of patients in the 5-mg arm, and 12.5% of patients in the placebo arm (Figure 4). The response rates for the 5- and 10-mg arms were both statistically significantly higher than the rate for the placebo arm. The secondary endpoint of ALP normalization was achieved by 27.3% of patients in the 10-mg arm, 5.4% of patients in the 5-mg arm, and no patients in the placebo arm. The investigators reported an absolute reduction in ALP of nearly 45% with the 10-mg dose, a decrease of approximately 122 units. Other serum liver tests reflected a similar benefit from seladelpar.

Adverse events were mild to moderate. The most common issues were pruritus (13% in the placebo arm, 3% in the 5-mg arm, and 11% in the 10-mg arm) and abdominal pain (3%, 9%, and 7%, respectively). A 52-week phase 3 study of seladelpar is scheduled to begin in early 2021.

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Real-World Effectiveness of Obeticholic Acid in Patients With Primary Biliary Cholangitis

Randomized studies have shown that UDCA, available since 1990, enables patients to live longer without liver transplantation.[1,2] In 2016, OCA was approved by the FDA as a second-line treatment for the many patients who do not respond to UDCA. OCA is a potent farnesoid X receptor agonist and a semi-synthetic derivative of chenodeoxycholic acid. Although OCA has been studied in clinical trials,[3] data on its real-world effectiveness are limited.

Dr Robert G. Gish and colleagues conducted a retrospective analysis on OCA in a real-world setting, and presented their findings in a poster at the AASLD 2020 Liver Meeting Digital Experience.[4] They examined data from adult patients diagnosed with PBC who received OCA between May 2016 and September 2019, using administrative claims and a laboratory database. The analysis reviewed biochemical responses to treatment. A total of 319 patients were included in the study; 290 (90.9%) were female, and 132 (41.4%) were 65 years of age or older, with varying numbers of patients tallied for each biochemical marker.

The researchers reported a trend toward lower mean values for several relevant markers of liver function. The follow-up duration was a mean of 11.6 months (± standard deviation [SD] 9.8). ALP, which measured 293 IU/L (± SD 193) at baseline, decreased to 239 (± SD 141) in the 177 patients with follow-up data. ALT dropped from 49 IU/L (± SD 37) to 38 IU/L (± SD 33) in the 179 patients with follow-up data. AST fell from 53 IU/L (± SD 35) to 45 IU/L (± 33) in the 178 patients with follow-up data. GGT changed from 229 IU/L (± SD 201) to 141 IU/L (± SD 161), and total bilirubin decreased from 1.1 mg/dL (± SD 1.6) to 0.9 mg/dL (± SD 1.1).

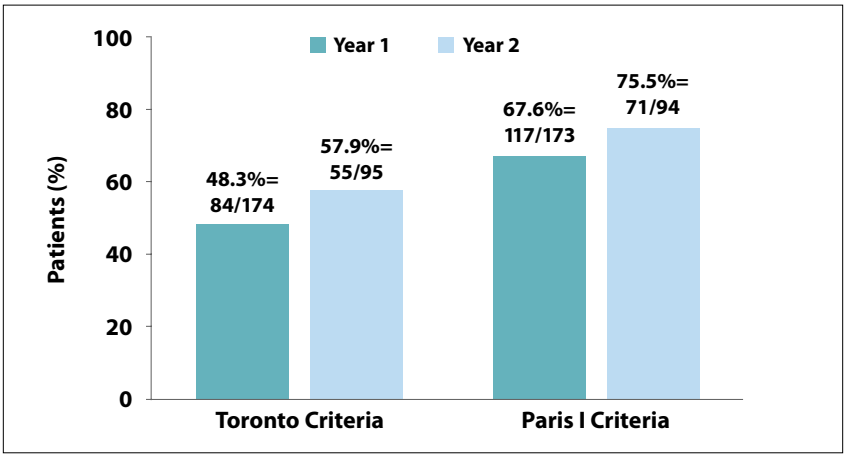

Figure 5. Proportions of patients with biochemical responses to obeticholic acid treatment during the follow-up periods. Adapted from Gish RG et al. AASLD abstract 1268. *Hepatology*. 2020;72(suppl 1).[4]

Figure 5 shows biochemical response to OCA over follow-up based on Toronto criteria (ALP ≤1.67 × ULN) and Paris I criteria (ALP ≤3 × ULN, AST ≤2 × ULN, total bilirubin ≤1.0 mg/dL).

The study was descriptive, and statistical significance was not considered. In addition, the data were culled from insurance claims, which are subject to possible coding errors. Nevertheless, the researchers concluded that the effectiveness of OCA was seen via decreases in biochemical markers of disease progression (ALP, ALT, AST, GGT, and bilirubin) in this real-world study of PBC patients and that the responses were sustained for up to 3 years.

ABSTRACT SUMMARY Efficacy and Tolerance of Obeticholic Acid in Patients With Primary Biliary Cholangitis and Inadequate Response to Ursodeoxycholic Acid in Real Life: Interim Analysis of the OCARELIFE Study

The France-based OCARELIFE study is evaluating the efficacy and tolerability of OCA in the real-life setting. An interim analysis (EASL FRI180) assessed outcomes among the 50 patients treated for 12 months. Most patients were female, and the mean age was 56 years. The primary endpoint was ALP response according to the Paris 2 criteria (Corpechot et al. *J Hepatol*. 2011;55[6]:1361-1367). At baseline, 17.1% (95% CI, 8.6%-25.6%) of patients met this criteria; at month 12, the rate was 40% (95% CI, 26.4%-53.6%). Liver tests showed significant improvement after 1 year of treatment. At an 18-month follow-up, total bilirubin had also improved. Pruritus was the most common adverse event and had decreased at month 12 compared to baseline.

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Results of a Phase 2, Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of Saroglitazar Magnesium in Patients With Primary Biliary Cholangitis (EPICS)

Saroglitazar magnesium is a PPAR-alpha and -gamma agonist that regulates both lipid and glucose homeostasis.[1,2] This novel drug is intended to break the cycle of cholestasis and inflammation that ultimately leads to the irreparable liver damage associated with PBC.

At the AASLD 2020 Liver Meeting Digital Experience, Dr Raj Vuppalanchi presented the results of a randomized, multicenter, phase 2 study of saroglitazar magnesium for the treatment of PBC.[3] The study began with a 6-week screening phase of an initial 81 patients previously treated with UDCA for at least 12 months. Levels of AST, ALT, and total bilirubin were screened upon study entry and again 4 weeks later. Patients whose ALP level was at least 1.67 times the ULN at both of these clinic visits were then randomized to receive 16 weeks of treatment with UDCA plus saroglitazar magnesium 2 mg (14 patients), UDCA plus saroglitazar magnesium 4 mg (13 patients), or placebo (10 patients).

The primary objective was to examine the effect of this treatment on ALP levels. The researchers also investigated the impact of saroglitazar magnesium treatment on liver biochemistries, lipid profiles, quality of life, and safety and tolerability. Four patients discontinued saroglitazar magnesium treatment due to adverse events, 1 in the 2-mg arm and 3 in the 4-mg arm, and 1 patient in the placebo arm withdrew consent.

At baseline, the mean ALP was 323 U/L ± 111 among the 13 analyzed patients in the saroglitazar magnesium 4-mg arm, 351 U/L ± 161 in the 2-mg arm (14 patients), and 295 U/L ± 73 in the placebo arm (10 patients). By the end of the study, ALP had decreased by an average of –163.3 U/L in the 4-mg arm, –155.8 U/L in the 2-mg arm, and –21.1 U/L in the placebo arm, making for a statistically significant reduction for both of the experimental treatment doses. In total, the mean percentage reduction of ALP was 48.9% in the 4-mg arm, 50.6% in the 2-mg arm, and 3.3% in the placebo arm (Figure 6).

The investigators also analyzed a composite endpoint that included ALP of less than 1.67 times the ULN, bilirubin of less than the ULN, and an ALP reduction of more than 15%. A total of 69% and 71% of patients in the 4-mg and 2-mg treatment arms, respectively, achieved this endpoint, compared to 10% of patients in the placebo arm. Patients reported favorable changes in fatigue and emotional difficulties. Patients across all 3 arms also noted cognitive and social changes; there were no noteworthy distinctions among the 3 arms. Adverse events in the 2 treatment arms centered on hepatic issues.

The researchers concluded that saroglitazar magnesium resulted in an estimated 50% decrease in ALP levels, with the reduction sustained, and that it had an acceptable toxicity profile. A phase 3 trial is currently being planned and will likely focus on a daily dosage of 1 and 2 mg.

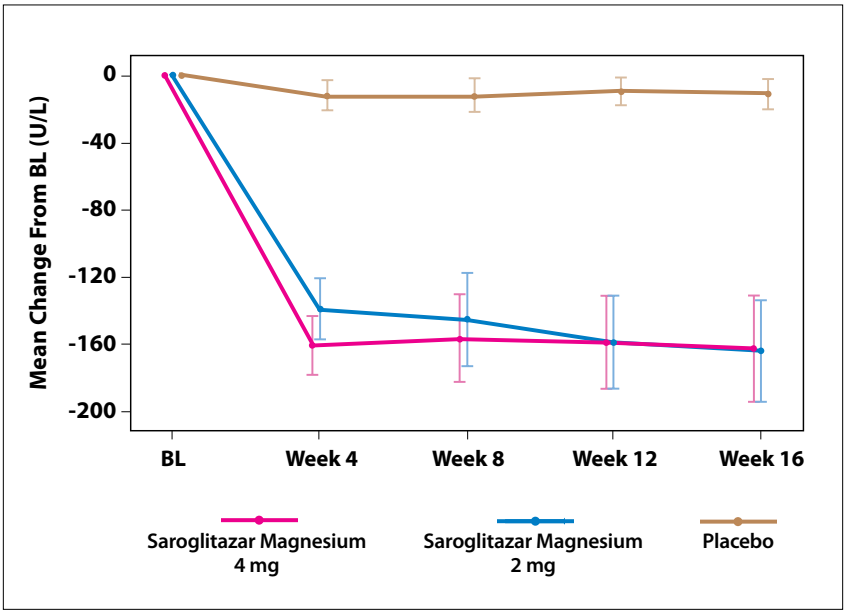

Figure 6. Effect on ALP (primary endpoint) with saroglitazar magnesium. ALP, alkaline phosphatase; BL, baseline. Adapted from Vuppalanchi R et al. AASLD abstract LO12. *Hepatology*. 2020;72(suppl 1).[3]

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Primary Biliary Cholangitis: Patient Characteristics and the Health Care Economic Burden in the United States

In the United States, the estimated prevalence of PBC is 39.2 cases per 100,000 individuals.[1] Most diagnoses are made between 30 and 60 years of age, and in women rather than men.[2] Although this chronic autoimmune disease is serious, culminating in end-stage liver disease if left untreated, there is limited research on the economic burden of PBC from a health care perspective.

In a poster at the AASLD 2020 Liver Meeting Digital Experience, Dr Gish and colleagues presented findings from a study that looked at the characteristics of individuals diagnosed with PBC, as well as at the economic burden of the disease on the US health care system.[3] The researchers identified 5157 patients diagnosed with PBC between May 1, 2016 and September 30, 2019, using a national database of administrative claims. To be included in the study, patients had to have had continuous medical insurance, including pharmacy benefits, for at least 6 months before their claims records began and up until either September 30, 2019 or their own disenrollment.

Of the 5157 patients whose data were included in the study, 3222 (62.5%) were 65 years of age or older and 4333 (84.0%) were female. All geographic regions in the United States were well represented, although the region with the most patients was the South (42.3%). The mean Charlson Comorbidity Index score was 3; 55.5% of patients had a score of 1 to 2, 23.4% of patients had a score of 3 to 4, and 21.1% of patients had a score of 5 or higher. The most common comorbidities included hypertension (53.6%), dyslipidemia (38.4%), and type 2 diabetes (24.3%). Other comorbidities included autoimmune hepatitis, rheumatoid arthritis, viral and/or chronic hepatitis, and alcoholic liver disease. The average follow-up time was 22.3 months (± SD 13.1).

In addition, the researchers evaluated health care costs for all causes and for PBC. The mean all-cause inpatient medical cost over a mean follow-up period of 22.3 months was $3905 per patient per month (Figure 7). An estimated 66% of this cost was due to PBC, an average of $2577 per patient per month. The mean total cost for all health care, which included inpatient hospitalizations, all outpatient services (office visits, emergency room visits, laboratory tests, and other procedures), and pharmacy costs, was $6568 per patient per month.

Coding errors were a possible limitation of this study. In addition, the patients included in the database may not have been representative of all patients diagnosed with PBC. The researchers concluded that the health care economic burden of PBC patients was substantial from a US health plan perspective, with costs related to PBC accounting for 44% of the mean total cost of care. Inpatient hospitalization costs related to PBC were a major contributor to the overall health care economic burden.

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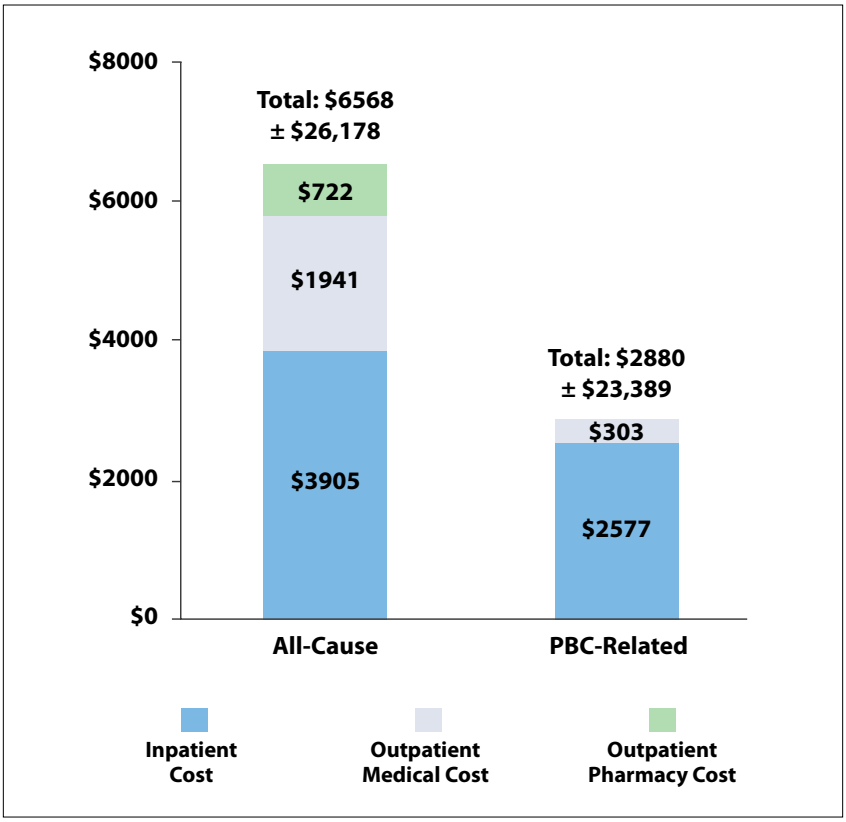

Figure 7. Health care costs PPPM during the follow-up period in 2019 US dollars among patients diagnosed with PBC. PBC, primary biliary cholangitis; PPPM, per patient per month. Adapted from Gish RG et al. AASLD abstract 1259. *Hepatology*. 2020;72(suppl 1).[3]

Bezafibrate Add-On Therapy Improves Liver Transplantation–Free Survival in Patients With Primary Biliary Cholangitis: A Japanese Nationwide Cohort Study

Among the agents being studied for PBC is bezafibrate. This agent is a pan-PPAR agonist that may be effective against cholestasis.[1] Bezafibrate may lead to changes in cholesterol, phospholipids, and bile acids. In addition, bezafibrate affects CYP3A4, in turn reducing bile acids, and targets toxic metabolites, xenobiotics, and bile acids. A study by Corpechot and colleagues investigated the rate of complete responses to bezafibrate compared with placebo, as well as the ability of the drug to reduce ALP levels, and demonstrated promising results.[2]

In Japan, bezafibrate at a dose of 400 mg per day has been used as a second-line approach for PBC since the 2000s, with usage steadily increasing over the years. To better understand whether this drug improves survival for patients with PBC, Dr Atsushi Tanaka and colleagues conducted a nationwide study, and the results were presented at the European Association for the Study of the Liver 2020 Digital International Liver Congress.[3]

The Japanese PBC cohort, established in 1980, is a collection of patient information gathered through surveys administered by the Japan PBC Study Group every 3 years. At the time of the analysis, the cohort included 9919 patients with PBC. Their average age was 57 years, and, as is typical of PBC, most patients were female.

Tanaka and colleagues analyzed numerous data points from this cohort. Among the total 8180 patients included in the evaluation, total bilirubin was 1.70 mg/dL in those who had never been treated (1133 patients), 1.04 mg/dL in those who had received UDCA only (6087 patients), and 0.96 mg/dL in those treated with bezafibrate (960 patients). ALP was 1.68 times the ULN in patients who had never been treated, 1.86 times the ULN in those who had received UDCA only, and 2.24 times the ULN in those treated

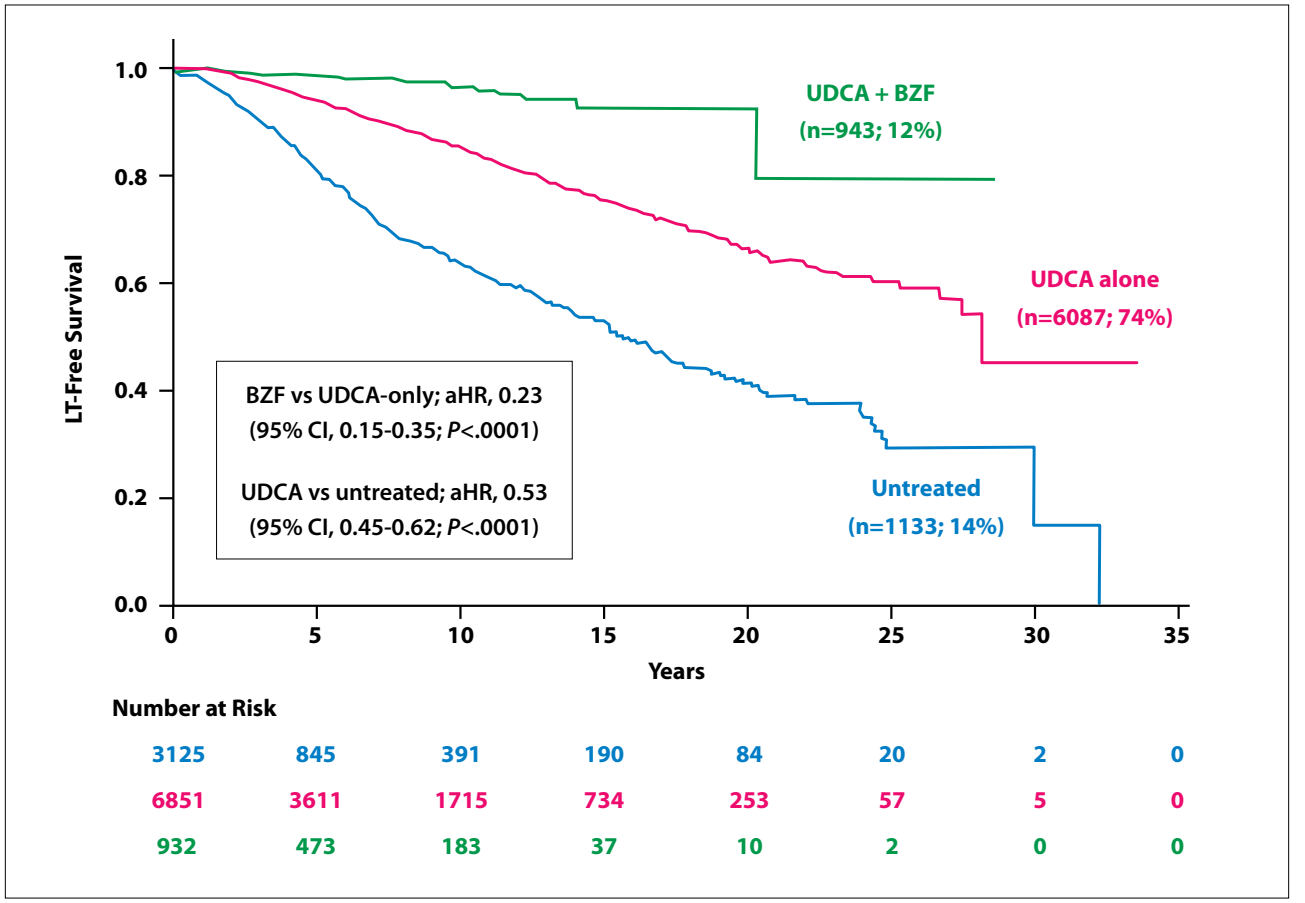

Figure 8. Survival curve according to treatment exposure. aHR, adjusted hazard ratio; BZF, bezafibrate; LT, liver transplantation; UDCA, ursodeoxycholic acid. Adapted from Tanaka A et al. EASL abstract GS01. *J Hepatol.* 2020;73(suppl 1).[3]

ABSTRACT SUMMARY Durability of Biochemical Improvements Through Six Years of Open-Label Treatment With Obeticholic Acid in Patients With Primary Biliary Cholangitis Who Did Not Achieve the POISE Criteria

This analysis (EASL abstract FRI146) looked at whether the 107 patients with PBC who did not reach the primary endpoint criteria in the POISE study could achieve a durable and meaningful response to OCA with extended treatment. With continued OCA, patients experienced a durable and significant reduction in ALP. Total bilirubin remained within the normal range, as did direct bilirubin. Other disease markers were also reduced, including ALT, AST, and GGT. Adverse events followed the same patterns seen in the POISE study, with pruritus and fatigue being the most common issues over the full 6-year study period. Long-term studies are needed to confirm whether these outcomes lead to a reduction in hepatic complications, the need for liver transplantation, and mortality rates.

with bezafibrate. It is important to note that 98% of patients treated with bezafibrate received this drug in combination with UDCA.

The researchers also looked at mortality data. According to their analysis, 37% of patients who had never been treated died of any cause and 28% died from liver-related issues. Among patients treated with UDCA, the death rates were 12% and 7%, respectively, and among patients treated with bezafibrate-containing therapy, the death rates were 3% and 2%, respectively. Figure 8 shows the survival curve according to treatment exposure.

Limitations of this study include the exclusion of significant numbers of patients from the analyses, unclear risk profiles of the patients who received bezafibrate compared with patients treated with UDCA, and the younger age and lower bilirubin of patients treated with bezafibrate compared with patients treated with UDCA (which may affect survival).

Tanaka and colleagues concluded that bezafibrate combination therapy is associated with a statistically significant reduction in both mortality and the need for liver transplantation in patients who had an incomplete response to first-line treatment with UDCA.

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GLIMMER Trial—A Randomized, Double-Blind, Placebo-Controlled Study of Linerixibat, an Inhibitor of the Ileal Bile Acid Transporter, in the Treatment of Cholestatic Pruritus in Primary Biliary Cholangitis

Cholestatic pruritus is a common issue for individuals diagnosed with PBC, and it detracts from quality of life.[1] Linerixibat, a minimally absorbed oral small molecule of the human ileal bile acid transporter, may treat cholestatic pruritus in this disease setting.[2,3]

An international group of researchers conducted a study to examine the dose response and tolerability of linerixibat for cholestatic pruritus in patients with PBC, and findings were presented in a poster at the AASLD 2020 Liver Meeting Digital Experience.[4] The researchers randomized 147 patients to treatment with a range of linerixibat doses—40 mg twice daily,

ABSTRACT SUMMARY The Pervasive Impact of Pruritus on Quality of Life in Patients With Primary Biliary Cholangitis: Real-World Experience in TARGET-PBC

This study assessed how pruritus affects quality of life for patients with PBC (AASLD abstract 1276). Using data from TARGET-PBC, a longitudinal, observational study that is ongoing at 38 sites across the United States, researchers evaluated the PBC-40, 5D Itch, and PROMIS Fatigue questionnaires. Itch that reached 7 points or higher on the itch domain (Mells et al. *Hepatology*. 2013;58[1]:273-283) was defined as clinically significant. Among the 211 patients who completed the PBC-40, 63% reported mild itch and 37% reported clinically significant itch. Patients with clinically significant itch reported more cognitive and social issues compared with patients who had only mild itch. These scores were an estimated 80% higher for the former group. Fatigue and emotional issues were also different between the 2 groups, but less so.

90 mg twice daily, 180 mg once daily, 20 mg once daily, and 90 mg once daily—or placebo. Linerixibat dose level assignments were determined according to ALP and total bilirubin levels. Treatment was single-blinded for 4 weeks, double-blinded for 12 weeks, and then single-blinded for a final 4 weeks, followed by a 4-week follow-up period.

The primary endpoint of the trial was the mean change from baseline in the mean score for worst daily itch, 16 weeks after study entry. The researchers also evaluated itch efficacy, quality of life (measured using the PBC-40 questionnaire), and pharmacodynamic biomarkers, as well as the safety and tolerability of linerixibat.

Most of the patients were female and over 50 years of age. Most patients were white, but approximately one-quarter were Japanese, East Asian, or South East Asian. Every morning and evening during the study, patients recorded their worst itch severity in an eDiary, using a numeric rating scale of 0 to 10; the worse of these scores was recorded as the worst daily itch.

All patients experienced a reduction in their worst daily itch score from baseline. For the placebo group (36 patients), that change was –1.73. The other groups had more dramatic reductions: –2.19 in the 20-mg once-daily group (16 patients), –2.60 in the 90-mg once-daily group (23 patients), –2.60 in the 180-mg once-daily group (27 patients), –2.86 in the 40-mg twice-daily group (23 patients), and –2.25 in the 90-mg twice-daily group (22 patients). The change in worst itch score between the start and end of the study was statistically significantly different between the placebo group and patients receiving linerixibat doses of 180 mg once daily, 40 mg twice daily, and 90 mg twice daily.

In terms of quality of life, only the group receiving 40 mg twice daily of linerixibat reported a statistically significant social and emotional improvement after 12 weeks. Regarding safety, 19% of patients in the placebo arm and 31% to 78% of patients in the treatment arms reported drug-related adverse events. The most common adverse event was diarrhea, experienced by up to 64% of patients, with 10% of patients withdrawing due to diarrhea or abdominal pain.

ABSTRACT SUMMARY Predicted Risk of End-Stage Liver Disease Utilising the UK-PBC Risk Score With Continued Standard of Care and Subsequent Addition of Obeticholic Acid for 60 Months in Patients With Primary Biliary Cholangitis

This analysis (EASL abstract THU114) evaluated the change in predicted risk of end-stage liver disease with the UK-PBC model in patients in the POISE study who had received placebo during the double-blind phase and then transitioned to OCA during the open-label extension for up to 60 months. Seventy-three patients were randomized to placebo; 70 completed the double-blind phase and 66 enrolled in the open-label extension. The UK-PBC risk score predicted a trend for increased risk of end-stage liver disease in PBC patients treated with placebo for 12 months in addition to standard of care. The addition of OCA reduced the predicted risk of end-stage liver disease for up to 60 months of treatment. This approach also led to sustained improvements in serum biochemistry.

ABSTRACT SUMMARY Final Data of the Phase 2a INTREPID Study With EDP-305, a Non–Bile Acid Farnesoid X Receptor Agonist

In the INTREPID study (AASLD abstract 1242), 68 patients with PBC were randomized to 12-week treatment with EDP-305, which has been shown to suppress liver injury and fibrosis in animal models, vs placebo. All patients were female and white, and the average age was 57 years. The intent-to-treat analysis found that among the 31 patients treated with EDP-305 1 mg, 45% experienced a response in ALP levels. For the 28 patients who received EDP-305 2 mg, that rate was 46%. By comparison, patients receiving placebo (9) had an ALP response rate of 11%. The absolute change in ALP among the EDP-305 arms was statistically significantly different from that seen with placebo. However, the study did not meet its primary endpoint of a 20% reduction in ALP.

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Highlights in Primary Biliary Cholangitis From the EASL 2020 Digital International Liver Congress, the ACG 2020 Virtual Annual Scientific Meeting, and the AASLD 2020 Liver Meeting Digital Experience: Commentary

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A number of important oral presentations and posters on primary biliary cholangitis (PBC) treatment were featured at the European Association for the Study of the Liver (EASL) 2020 Digital International Liver Congress, the American College of Gastroenterology (ACG) 2020 Virtual Annual Scientific Meeting, and the American Association for the Study of Liver Diseases (AASLD) 2020 Liver Meeting Digital Experience. Data were presented on various therapies, including obeticholic acid (OCA), seladelpar, bezafibrate, linerixibat, and saroglitazar magnesium.

Long-Term Open-Label Treatment With OCA in POISE Trial Participants

Several abstracts presented at these meetings pertained to the long-term efficacy and safety, or durability of response, of open-label OCA after patients completed the POISE trial. OCA, which is a farnesoid X receptor (FXR) agonist, is the only medication approved as second-line treatment for PBC at the present time in the United States. The POISE trial was a phase 3 trial in which patients were randomized to placebo, OCA 5 mg titrated up to 10 mg at 6 months, or OCA 10 mg daily for 12 months. The primary endpoint was the composite endpoint of a reduction in alkaline phosphatase (ALP) to less than 1.67 times the upper limit of normal (ULN) with at least a 15% reduction in ALP and maintenance of bilirubin at less than the ULN. At the end of 1 year, 46% to 47% of the patients treated with OCA 5 mg titrated to 10 mg or 10 mg daily showed a response meeting this composite endpoint.[1] Subsequently, there was a long-term, open-label, safety extension study for up to 72 months, in which patients received OCA 5 to 10 mg daily. In an oral presentation at the 2020 ACG meeting, Dr Christopher L. Bowlus presented data showing that the likelihood of response to OCA in the long-term, safety and efficacy open-label study essentially did not differ in terms of sex or age.[2] Although the number of patients (particularly men) was small, making it difficult to draw conclusions, the broad interpretation of this analysis was that the likelihood of patients having a response appeared to be similar across all of the demographic subgroups studied (male, female, patients ≤47.5 years at diagnosis, patients >47.5 years at diagnosis, patients ≤55 years at study entry, and patients >55 years at study entry).

In addition, Dr Bowlus and colleagues presented a poster at the 2020 AASLD meeting that looked at response across biochemical groups.[3] At study entry, patients were subclassified depending on whether they had an ALP of no more than 3 times the ULN vs greater than 3 times the ULN, as well as a total bilirubin of no more than the ULN vs greater than the ULN. Patients in all biochemical subgroups had a response, and improvement with OCA was more pronounced in patients with a higher bilirubin and ALP at baseline. Interestingly, discontinuation due to pruritus was uncommon in this population (only approximately 4%).[3]

At the 2020 EASL meeting, Dr Gideon M. Hirschfield and colleagues presented a poster that examined the durability of biochemical response in patients with PBC who did not achieve the POISE criteria.[4] The researchers found that there was a significant and durable decrease in ALP (P<.01 at all time points) during the 72 months of open-label treatment in patients who did not achieve the POISE criteria after 12 months of OCA. Also at all time points, there was a significant reduction in aspartate aminotransferase (P<.05), alanine aminotransferase (P<.01), and gamma-glutamyl transferase (P<.05), suggesting that even patients who did not achieve the POISE endpoint criteria may have possible benefit from OCA treatment.

The takeaway from these studies on the long-term follow-up of the POISE open-label extension is that different subpopulations, based on liver biochemical tests, age, and sex, demonstrate a similar response to long-term treatment with OCA. An important caveat to the long-term extension study is that there was no placebo control population. Nevertheless, these results suggest that long-term OCA treatment among POISE trial participants was safe and well tolerated and demonstrates long-term

efficacy in improving serum ALP and other liver biochemical tests.

Other Data Involving OCA

Dr Robert G. Gish and colleagues presented a poster at the 2020 AASLD meeting that examined the real-world efficacy of patients treated with OCA in the clinic setting in a nonclinical trial environment.[5] The authors found that the Toronto criteria (a reduction of ALP to ≤1.67 × ULN) were achieved in approximately 48% and 58% of patients treated with OCA at 1 and 2 years, respectively. However, there was no control arm, baseline values were not clearly available, and a heterogeneous range of laboratories may have been used for tests because this was a real-world study. Nevertheless, these data show that response to OCA treatment in the "real-world," community setting appears to be similar to clinical trial findings.

PPAR Agonists

Seladelpar

In a late-breaking oral session at the 2020 AASLD meeting, Dr Hirschfield presented data on seladelpar, a peroxisome proliferator-activated receptor (PPAR)-delta agonist, from the phase 3 ENHANCE trial.[6] Other PPAR agonists that have been studied for PBC include bezafibrate (which is not available in the United States but is available in Japan and Europe, although it is not licensed for PBC there), fenofibrate (which is available in the United States but is not approved for the treatment of PBC), and elafibranor (a dual PPAR-alpha and -delta agonist). The response criteria used in the ENHANCE trial were the same as those used in the POISE trial[1] (a composite endpoint of reduction of ALP to <1.67 × ULN with ≥15% reduction in ALP and a normal bilirubin). Unexpected liver histologic findings in a separate study in nonalcoholic steatohepatitis (NASH) caused all seladelpar trials to be placed on hold to determine whether these findings were associated with seladelpar treatment.[7] A consensus group of clinicians and pathologists subsequently reviewed liver biopsies from the NASH trial and found that there were no new histopathologic lesions that were of concern[8]; following this announcement, another phase 3 trial of seladelpar is planned. The AASLD presentation[6] included the available 3- and 6-month data from the phase 3 seladelpar PBC trial prior to the interruption of the study. The composite endpoint was reached by 78.2% of patients treated with seladelpar 10 mg vs 12.5% of patients on placebo (P<.0001). In addition, 27.3% of patients on seladelpar 10 mg vs 0% on placebo experienced normalization of ALP by 3 months (P<.0001). Treatment with seladelpar 10 mg also resulted in a statistically significant improvement in pruritus (P<.05) for patients with moderate-to-severe itch at baseline vs placebo. Overall, seladelpar appeared to be safe and well tolerated in this study. Pruritus occurred in 12.6%, 3.4%, and 11.2% of the placebo, 5-mg, and 10-mg groups, respectively. There were no reports of treatment-related serious adverse events, but treatment-emergent adverse events led to study discontinuation in 2 patients treated with placebo, 2 patients treated with seladelpar 5 mg, and 2 patients treated with seladelpar 10 mg.

Bezafibrate

Dr Atsushi Tanaka presented data at the 2020 EASL meeting from a long-term registry of over 9000 patients with PBC who have been followed in Japan.[9] The aim of the study was to examine whether adding bezafibrate, a pan-PPAR agonist, to ursodeoxycholic acid improved long-term outcomes. Because this was a long-term, large population study, it was possible to evaluate clinical outcomes in patients treated with bezafibrate in addition to ursodeoxycholic acid, rather than surrogate endpoints such as improvement in ALP. Dr Tanaka and colleagues reported a hazard ratio of 0.55 in liver-related mortality or the need for liver transplantation for patients treated with ursodeoxycholic acid. When bezafibrate was added to ursodeoxycholic acid, the hazard ratio was 0.21, corresponding to a 79% reduction in the risk of death or the need for liver transplantation.

This study was performed in Japan and so may not be generalizable to the PBC population worldwide. Nevertheless, these data are compelling and demonstrate that ursodeoxycholic acid improved long-term clinical outcomes in PBC patients from a population perspective. This study also supports the concept that the addition of a second agent, in this case bezafibrate, may further improve clinical outcomes in patients.

A study presented at the 2019 EASL meeting showed that the dual PPAR agonist elafibranor showed improvement in ALP and possibly pruritus in a phase 2 trial.[10]

New Drugs in Development

Linerixibat

Dr Cynthia Levy and colleagues presented a poster at the 2020 AASLD meeting on the ileal bile acid transporter (IBAT) inhibitor linerixibat for the treatment of pruritus.[11] In the phase 2, placebo-controlled, dose-finding GLIMMER trial, the authors found evidence of dosing-related changes in fibroblast growth factor 19 and in C4 with treatment, suggesting that there was target engagement with this IBAT inhibitor. Treatment with linerixibat was also associated with improvement in pruritus, and twice-daily treatment seemed more effective. The main side effect in the GLIMMER trial was diarrhea, which occurred in 8% to 64% of the treated patients.

EDP-305

My colleagues and I had the opportunity to present data on the FXR agonist EDP-305 in a poster at the 2020 AASLD meeting.[12] Two doses were studied: 1 and 2.5 mg. The primary endpoint was a reduction in ALP of at least 20%. Although there was a trend toward a dose-related response in terms of reduction in ALP in patients treated

with EDP-305, the reduction was not statistically significant. However, in a post hoc analysis of patients who completed treatment and in whom no data were missing, EDP-305 was associated with a dose-related significant reduction in ALP. The main adverse event associated with EDP-305 in PBC was dose-related pruritus, which did affect the response rate.

Saroglitazar Magnesium

In a late-breaking session at the 2020 AASLD meeting, Dr Raj Vuppalanchi presented phase 2 data on 2 or 4 mg of the PPAR-alpha and -gamma dual agonist saroglitazar magnesium vs placebo.[13] The inclusion criteria were patients with PBC who were 18 to 75 years of age and were intolerant, or had a suboptimal response, to ursodeoxycholic acid. The entry criteria were an ALP of at least 1.67 times the ULN and a less-than-30% variation between visits 1 and 2. The mean percentage reduction of ALP was 48.9% with 4 mg of saroglitazar magnesium and 50.6% with 2 mg of saroglitazar magnesium. The composite endpoint, the same as in the POISE and ENHANCE trials,[1,6] was achieved in 69% of the 4-mg group, 71% of the 2-mg group, and 10% of the placebo group.

The improvement in symptoms appeared to be dose-related, with a comparable reduction in itching in both the 2- and 4-mg groups. It was noted that serum alanine aminotransferase rose to more than 3 times the baseline value in 3 patients in the 4-mg arm and 1 patient in the 2-mg arm. A hepatic safety adjudication committee found that there was a probable relationship between this increase and saroglitazar magnesium in the 3 patients on 4 mg and a possible relationship in the patient on 2 mg. No cases met Hy's Law criteria for drug-related hepatotoxicity, and ALP declined with treatment in all 4 cases.

TARGET-PBC

A poster at the 2020 AASLD meeting by the TARGET-PBC Study Group highlighted the effect of pruritus on quality of life in PBC.[14] Of 667 patients with PBC, 30% reported clinically significant itching using the PBC-40 scoring system. Patients with clinically significant itch also had clinically significant fatigue, more than 50% of patients reported cognitive impairment, and over 25% of patients reported social difficulties. This study highlights pruritus as an important symptom that negatively affects quality of life in patients with PBC, as well as the need for therapies that both modify the progression of the disease and improve symptoms and patient-reported outcomes.

Conclusion

Many new therapies are currently in clinical trials for the treatment of PBC, and long-term data on the safety and efficacy of OCA in PBC are now available. It is hoped that additional therapies in combination with ursodeoxycholic acid may make it possible to achieve complete biochemical remission in patients with PBC, and that these regimens will be safe and well tolerated and will curtail the natural history of this disease, as well as improve symptoms and quality of life.

Disclosures

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