Response to Low Dose of Obeticholic Acid in Primary Biliary Cholangitis in the Real-World Population

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ABSTRACT

The objective of this study is to assess the real-world efficacy and safety of a 5 mg/day dose of obeticholic acid (OCA) in patients with primary biliary cholangitis (PBC). For this, a retrospective observational study was carried out. The primary endpoint was defined as alkaline phosphatase (AP) levels below the 1.67 upper limit of normal (ULN) with more than a 15% reduction from baseline, along with normal total bilirubin (TB) levels. The 'secondary endpoint' was the biochemical response of alanine (ALT) and aspartate (ASP) aminotransferases. The sample was composed of 26 patients who received 5 mg of OCA daily. Baseline ALP levels were below1.67 ULN in 33% of patients. After 48 months of treatment, the proportion of patients with ALP <1.67 ULN increased to 45%, from a basal percentage of 33%, remaining stable throughout the 50-month study period. Regarding ALT and AST, 30-40% of patients had levels <1.67 ULN at baseline. By month 36, 100% of patients had normalized these levels. In conclusion, treatment with 5 mg/day of OCA achieved ALP improvement in 12% (from a basal percentage of 33% to 45% at the end of study period) of patients over 50 months. The treatment also normalized ALT and AST levels in a high proportion of patients.

Key Words: *Alanine aminotransferase, Alkaline phosphatase, Aspartate aminotransferase, Obeticholic acid, Primary biliary cholangitis*

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INTRODUCTION

Primary biliary cholangitis (PBC), also known as chronic nonsuppurative destructive cholangitis and previously referred to as primary biliary cirrhosis, is a rare autoimmune liver disease that predominantly affects middle-aged women [1]. Ursodeoxycholic acid (UDCA) monotherapy at a dose of 13–15 mg/kg of body weight per day is the gold standard for first-line treatment of PBC [2]. However, some patients do not respond adequately to this treatment, which led to the conditional approval of obeticholic acid (OCA) in 2016 as a second-line therapy for patients with an inadequate response or intolerance to UDCA [3]. Normalization of serum alkaline phosphatase (ALP) has been shown to correlate with a better prognosis in PBC [4].

The objective of this study is to assess the real-world efficacy and safety of a 5 mg/day dose of obeticholic acid (OCA), instead of the standard 10 mg, in patients with primary biliary cholangitis (PBC), aiming to reduce the risk of side effects commonly linked to OCA. The study relies on data from routine clinical practice rather than controlled trials, with a focus on evaluating liver biochemical markers (e.g., alkaline phosphatase, and bilirubin levels).

MATERIALS AND METHODS

This retrospective study collected data from the PBC Registry of Aragón (Spain), an ongoing, non-interventional observational cohort study that monitors patients with PBC treated with OCA as second-line therapy, in tertiary centers across Spain.

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Patients included had ALP ≥1.67 ULN and/or bilirubin levels between 1 mg/dL and 2 mg/dL after at least 12 months of UDCA treatment or had UDCA intolerance. Adult patients diagnosed with PBC who started OCA treatment between September 2019 and February 2024, with a minimum follow-up of 50 months, were included.

Demographic, clinical, and biochemical data were collected at baseline and every three months for up to 50 months. The primary endpoint was defined as ALP levels below 1.67 ULN with more than a 15% reduction from baseline, along with normal total bilirubin (TB) levels. Secondary endpoints included the biochemical response of ALT and ALP. The primary composite endpoint was based on POISE [5] and COBALT [6] criteria. The 'secondary endpoint' was the biochemical response of alanine (ALT) and aspartate (ASP) aminotransferases and TB at OCA therapy [7].

Data were captured using baseline and follow-up case laboratory records, completed by physicians in each collaborating center. Demographic, clinical, and biochemical data were collected at baseline (immediately before starting OCA therapy), and consecutively each 3 months up to 50 months of follow-up.

As the study was retrospective and non-experimental, with pooled data obtained from secondary sources, and carried out in a Spanish public hospital, review by an ethical committee was not necessary. However, this research adhered to the ethical guidelines outlined in the 1975 Declaration of Helsinki, updated in 2013.

Continuous variables were described by mean (±standard deviation). To compare groups, we used the X^2 test for categorical variables (or Fisher exact test in the case of sparse data) and the Student t test for continuous variables (or Wilcoxon test when a significant departure from normality was detected).

RESULTS AND DISCUSSION

The sample included 26 patients **(Table 1)**.

Table 1. General characteristics of the study cohort.

Characteristic N = 26	
Sex, female, n (%)	25 (88)
Age at diagnosis, years (mean)	56 (8.2)
Age at OCA start, years (mean)	59.4 (8.6)
AMA positivity, n (%)	21 (81)
UDCA use, n (%)	26 (100)
UDCA dose, mg/kg	15.0
Indication to OCA start (% patients)	
Intolerance to UDCA	0
Inadequate response to UDCA	100
OCA dose, 5 mg daily	100
ALP<1.67 ULN at baseline	33
ALT<1.67ULN at baseline	29
AST<1.67ULN at baseline	43
Total bilirubin<1ULN at baseline	14

All patients received 5 mg of OCA daily. None had an intolerance to UDCA, but all had an inadequate response. Baseline ALP levels were below 1.67 ULN in 33% of patients. After 48 months of treatment, the proportion of patients with ALP <1.67 ULN increased to 45%, remaining stable throughout the 50-month study period **(Figure 1)**.

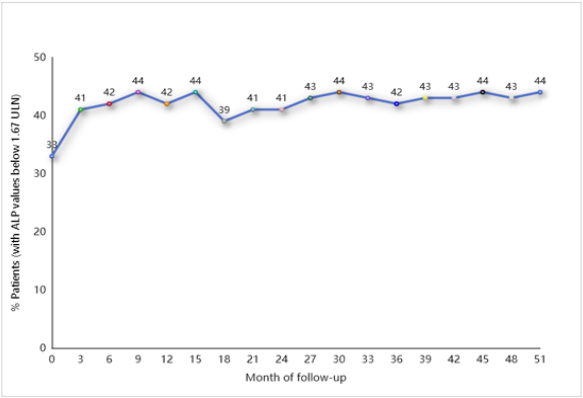

Figure 1. Evolution of the percentage of patients with alkaline phosphatase (ALP) values <1.67 ULN.

Regarding ALT and AST, 30-40% of patients had levels <1.67 ULN at baseline. By month 36, 100% of patients had normalized these levels. BT also significantly decreased with OCA treatment, representing a surrogate marker for long-term survival **(Figure 2)**.

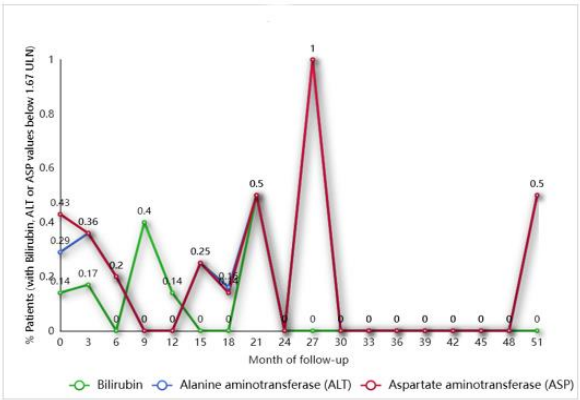

Figure 2. Evolution of the ratio of patients with ALT or AST values <1.67 ULN vs. total patients, every 3 months; and the ratio of patients with total bilirubin >1 ULN vs. total patients.

UDCA remains the standard of care for PBC, with a 10-year liver transplant-free survival rate of 79.7% in patients treated with it. However, 20-40% of patients do not fully

respond to this treatment, highlighting the need for alternatives like OCA.

Our results align with previous studies, showing that 45% of patients achieved ALP <1.67 ULN, from a basal percentage of 33% to 45% at the end of study period (a non-statistically significant difference (95% CI: -13.7895% to 35.7100%; Chi-squared: 0.772; significance level P: 0.3797)), without the need to escalate the OCA dose to 10 mg. This is comparable to studies such as Luo *et al*. which demonstrated OCA's efficacy in patients with poor UDCA response, though associated with a higher incidence of adverse events, particularly pruritus and fatigue [8].

CONCLUSION

Treatment with 5 mg/day of OCA achieved ALP improvement in 12% of patients (from a basal percentage of 33% to 45% at the end of study period), maintaining this improvement over 50 months. The treatment also normalized ALT and AST levels in a high proportion of patients. Despite advances in second-line therapy for PBC, there remains a need for more effective treatments for patients at higher risk of disease progression.

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Conflict of interest: None

Financial support: None

Ethics statement: As the study was retrospective and non-experimental, with pooled data obtained from secondary sources, and carried out in a Spanish public hospital, review by an ethical committee was not necessary. However, this research adhered to the ethical guidelines outlined in the 1975 Declaration of Helsinki, updated in 2013.

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