

Long-term effectiveness, safety, and liver stiffness dynamics of PBC treatment with obeticholic acid in real-world

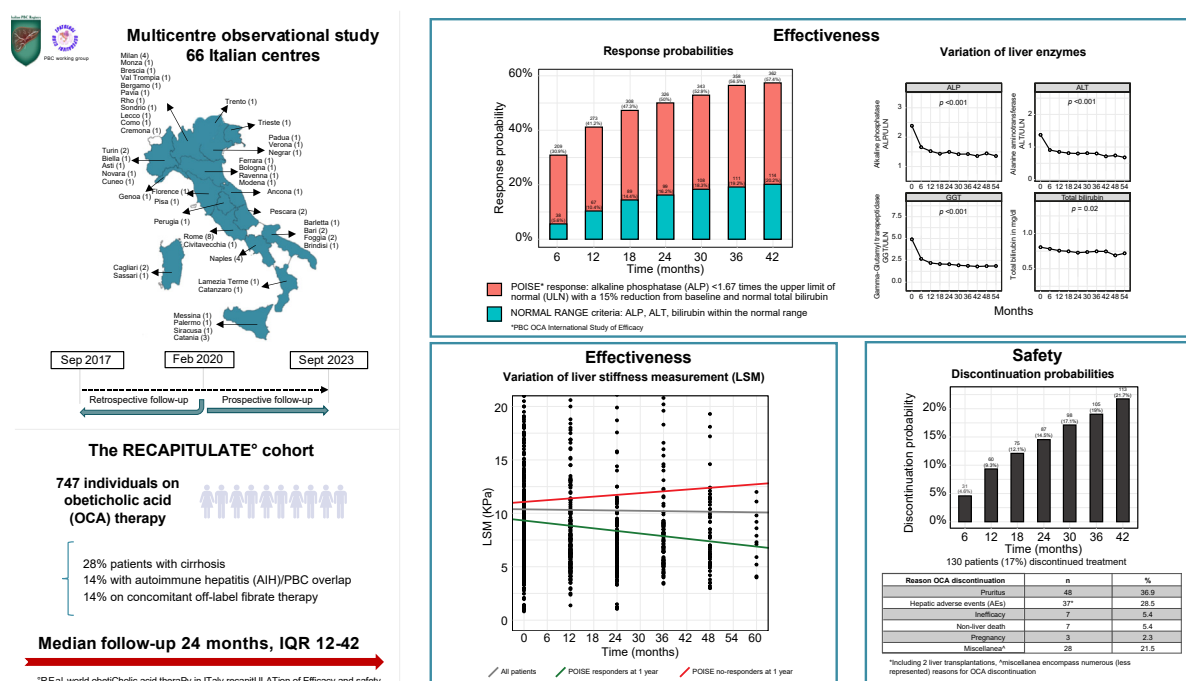
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Graphical abstract



Highlights:

- Latest results from the largest real-world OCA-treated PBC cohort confirm its biochemical effectiveness in the medium/long term.
- Patients with compensated cirrhosis show equally good responses but higher likelihood of hepatic events leading to discontinuation.
- Patients with AIH/PBC overlap exhibit an effectiveness/safety profile comparable to those with PBC alone.
- The original data on liver stiffness variation under OCA therapy demonstrate that its trend depends on drug response.

Impact and Implications:

After the conditional approval of OCA for the treatment of PBC, the main confirmatory study failed to demonstrate OCA's ability to reduce liver-related events, leading the EMA to revoke the drug's marketing authorization. The ensuing scientific debate highlights an urgent need for further evidence from real-world practice. In the largest real-world series of patients treated with OCA to date, we confirm that the drug's effectiveness and safety profiles are maintained over a medium-to-long follow-up period. Valuable data for the management of the drug in relevant subgroups of patients, such as those with cirrhosis and autoimmune hepatitis/PBC overlap syndrome, are also provided. Our original results on liver stiffness measurement variation over time suggest a favourable impact of OCA on fibrosis progression, particularly in patients achieving a biochemical response to the drug. Overall, these data provide important insights for clinicians managing patients with PBC and contribute to the ongoing scientific debate about the effectiveness/safety profile of this drug.

Long-term effectiveness, safety, and liver stiffness dynamics of PBC treatment with obeticholic acid in real-world

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Background & Aims: Several studies have assessed the short-term effectiveness and safety of obeticholic acid (OCA) in the real-world setting. We aimed to extend knowledge on the real-world effectiveness and safety of OCA treatment by expanding sample size and follow-up, and by exploring changes in liver stiffness measurement (LSM) over time.

Methods: The RECAPITULATE project involves centres belonging to the "Italian PBC registry" and/or the "Club Epatologi Ospedalieri" PBC working group. Effectiveness was evaluated as biochemical response according to POISE and normal range (NR) criteria (normal alkaline phosphatase/alanine aminotransferase/bilirubin). Safety was assessed as the incidence of *de novo*/worsening pruritus and discontinuation rate/causes. Available LSMs were also captured.

Results: We included 747 patients from 66 Italian centres: mean age 58 years; female/male 88%/14%; median follow-up 24 months [IQR 12–42]; 28% with cirrhosis, and 14% with autoimmune hepatitis (AIH)/PBC overlap syndrome. Probabilities of POISE and NR response increased from baseline to 57% and 20%, respectively, by the 42nd month. The probabilities of response were lower in patients with cirrhosis ($p = 0.02$ and $p = 0.004$ for POISE and NR), but not different between patients with AIH/PBC and pure PBC ($p = 0.8$). Overall, 130 patients (17%) discontinued treatment, mainly due to pruritus (36.9%), while 28.5% did so after developing hepatic events. The discontinuation rate was higher in patients with cirrhosis ($p < 0.001$). LSM was available in 573 patients (~77%), of whom 255 had multiple measurements. LSM variation over time differed based on the attainment of POISE biochemical response (expected mean annual variation -0.48 [$-0.78, -0.19$] in responders vs. $+0.33$ [$-0.07, 0.73$] in non-responders, respectively, $p < 0.001$).

Conclusions: Our findings confirm the effectiveness and safety profiles of OCA in the medium/long term and demonstrate that biochemical response is associated with the change in LSM over time.

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Introduction

Primary biliary cholangitis (PBC) is a chronic cholestatic autoimmune liver disease that leads to progressive destruction of small bile ducts and subsequent cholestasis. If untreated or under-treated, it can progress to liver fibrosis, cirrhosis, and its complications, including the need for liver transplantation.^{1,2} Ursodeoxycholic acid (UDCA), at a dose of 13–15 mg/kg/day, is the first-line therapy, as it has been demonstrated to improve liver biochemistry, histology, and transplant-free survival.^{3,4} However, 25–40% of patients do not respond to UDCA therapy.^{5,6}

In 2016, the FDA and EMA conditionally approved obeticholic acid (OCA) as a second-line treatment for patients with PBC who do not respond or are intolerant to UDCA.^{1,7} OCA is a semi-synthetic derivative of chenodeoxycholic acid with farnesoid X receptor agonist activity. It is protective against cholestasis through its pleiotropic action on bile acid synthesis and transport, as well as having anti-inflammatory and anti-fibrotic properties.^{8,9} Accelerated approval of OCA by the FDA and conditional approval by the EMA were based on the results of the PBC OCA International Study of Efficacy (POISE) trial and its open-label extension.^{10,11} The trial demonstrated that OCA treatment led to sustained reduction and/or stabilisation of the main prognostic determinants in PBC, namely alkaline phosphatase (ALP) and bilirubin.^{10,11} Nevertheless, a full approval by the EMA would have required a subsequent demonstration that the drug reduced the incidence of liver-related events. Unfortunately, the trial designed for this purpose, *i.e.* the Clinical Outcomes with Obeticholic Acid in Liver Treatment (COBALT) trial, was prematurely terminated based on feasibility issues related to patient recruitment and retention after OCA became commercially available.¹²

Notably, in the restricted study sample population, OCA failed to demonstrate any benefit compared to placebo on the incidence of PBC-related outcomes. Based on this, on 28th June 2024, the EMA Committee for Medicinal Products for Human Use (CHMP) recommended revoking the marketing authorization for OCA, a decision that became definitive and operational starting from 30th August 2024. Currently, this position by the EMA is causing significant scientific and regulatory debate. The discussion involves not only the specific biases and results of the COBALT trial but also, more generally, the possibility of drawing on alternative evidence to randomized placebo-controlled clinical trials to generate evidence in the field of rare diseases.¹³

From this perspective, since OCA approval, a number of real-world studies have evaluated its effectiveness and safety in the post-marketing phase.^{14–17} Real-world studies always provide a highly relevant perspective on the usage and outcomes of any drug in everyday clinical practice. Indeed, compared to registrational trials, these studies include more heterogeneous populations, less selected and with a higher rate of comorbidity, in which the drug under observation is used according to less rigid and more personalized regimens and dosages based on the experience of the referring clinician.¹⁸ Altogether, data from real-world cohorts of patients with PBC treated with OCA have substantially confirmed the results of the registrational trial, adding some relevant information for the management of specific subgroups of patients.^{14–17} However, the main limitations of these series were represented by the relatively small sample sizes and, mainly, by the short duration

of follow-up.^{14–17,19,20} Indeed, until not long ago, the only available studies exploring OCA treatment in the medium/long-term are the open-label extension of the POISE trial and two recent real-world studies, one extending the original IBER-PBC cohort and one from the Spanish ColHai registry.^{11,19,20} More recently, the COBALT trial has also been published,²¹ and other studies that foresee the long-term use of OCA are ongoing.^{22,23} Additionally, works have been presented in which the outcomes of patients treated with OCA are compared with control cohorts in analyses designed to emulate clinical trials.^{24,25} Just as the sample size is essential to ensure the robustness of results, the duration of follow-up provides indispensable information for understanding the management of a chronic disease like PBC. Moreover, data on the kinetics of liver stiffness measurements (LSM) during OCA treatment are limited.

Based on this background, we herein aimed to provide medium/long-term real-world results from the largest series of patients with PBC exposed to OCA treatment described so far, including the variation of LSM over time in relation to the biochemical response to the drug.

Patients and methods

Study design and participants

This is a multicentre, observational, mixed retrospective/prospective study, in which data were initially captured retrospectively (from September 2017 to January 2020), and then prospectively (from February 2020 to September 2023). Centres belonging to the “Italian PBC registry” and/or to the “Club Epatologi Ospedalieri” (CLEO) PBC working group were invited to join the REal-world obetiCholic Acid theraPy in ITaly recapitULATION of Efficacy and safety (RECAPITULATE) project. Centres participating in the study were asked to include all adult patients: i) diagnosed with PBC but either intolerant or with inadequate response to 1 year of UDCA treatment (ALP >1.5x the upper limit of normal [ULN] and/or bilirubin levels >ULN but less than 2x ULN, according to Italian OCA prescriptive rules); ii) who had received at least one dose of OCA. Patients with Child-Pugh (CP) class A cirrhosis, those with autoimmune hepatitis (AIH)/PBC overlap syndrome and those receiving off-label fibrate therapy before or after OCA start were not excluded. Exclusion criteria were CP class B/C cirrhosis or a history of decompensation – according to the restrictions imposed in Europe regarding the use of OCA – or having been previously enrolled in a clinical trial with OCA. The administration and dosage of OCA therapy were managed independently by each physician, based on the package insert, personal experience and adapted to patient’s tolerance.

Diagnosis of PBC and AIH/PBC overlap syndrome was established according to EASL guidelines.¹ Diagnosis of cirrhosis was based on the following criteria: i) liver histology; and/or ii) LSM assessed by vibration-controlled transient elastography ≥ 16.9 kPa; and/or iii) physician judgement based on a combination of anamnestic (previous decompensating events, such as ascites, variceal bleeding, encephalopathy), radiological (liver surface nodularity, caudate lobe hypertrophy, enlarged spleen, or other signs of portal hypertension), endoscopic (presence of gastro-oesophageal varices) and/or laboratory findings (low platelets, low albumin, prolonged prothrombin time or international normalised ratio).^{26,27}

The study was conducted under the Declaration of Helsinki guidelines and the principles of good clinical practice. All participants provided written informed consent. The study was approved by the University of Milan-Bicocca research ethics committee (Study name: PBC322), the coordinator of the Italian National Registry, and the Research and Development Department of each collaborating hospital.

Data collection

Data were captured by physicians using electronic case record forms. Demographic, anthropometric, and liver disease assessment data were collected at baseline, while OCA dose adjustments and discontinuation, liver biochemistry, and assessment of pruritus were collected at baseline and at each time point (every 6 months).

Follow-up started on the date of OCA initiation and ended on the date of OCA discontinuation or at the time of last observation. Consistently, the entire follow-up coincided with the time on OCA therapy.

Cases in which, after 6 months of treatment, patients were not up-titrated from 5 mg/day to 10 mg/day even though they were not responding according to POISE criteria and had not experienced *de novo* or worsening pruritus, were defined as missed up-titrations.

Clinically relevant pruritus was systematically assessed and classified as mild, moderate, or severe as follows: mild, pruritus of mild intensity or localised, or under treatment for pruritus with residual pruritus absent or mild; moderate, pruritus of moderate intensity or diffuse but intermittent; severe, pruritus of severe intensity or diffuse and continuous. Moreover, pruritus was classified as '*de novo*' if it occurred after the start of OCA treatment, or as '*worsening*' if present at baseline but increased on OCA therapy. Adverse events (AEs) were not systematically assessed but registered when they led to permanent drug discontinuation.

When available, LSMs measured by vibration-controlled transient elastography were systematically collected. LSMs with an IQR/median ratio >30% were considered unreliable and excluded from the analyses.

Completed case record forms underwent quality control for completeness and accuracy at the University Campus Bio-Medico, Rome. Missing, inaccurate, or implausible data were systematically queried with the treating physicians.

Study endpoints

The primary effectiveness endpoint was the biochemical response according to the POISE criteria, *i.e.* ALP <1.67x ULN with a reduction of ≥15% from baseline and a normal total bilirubin level (<1 mg/dl). The secondary endpoint was the biochemical response according to 'normal range' (NR) criteria, defined as alanine aminotransferase (ALT), ALP, and total bilirubin within the normal ranges. Other effectiveness endpoints included the variation of ALP, gamma-glutamyltransferase (GGT), ALT, aspartate aminotransferase (AST), and total bilirubin levels, as well as the variation of LSMs over time.

The safety endpoints were the incidence of *de novo* clinically relevant pruritus or worsening of pre-existing pruritus, and the discontinuation rate, with associated timing and causes of discontinuation. As in clinical trials, every event that led to discontinuation of OCA was reported as an AE, regardless of whether it was attributable to the drug itself or not.

Statistical analysis

General socio-demographic and clinical characteristics were described by means of descriptive statistics. To account for inter-laboratory variability, ALP, GGT, AST and ALT were expressed as ratios of their respective ULN. Variables with ≤5% missing values were imputed with random forests using the MissRanger package in R. Conversely, variables with ≥20% missing values were not considered due to the low representativeness of the whole sample. When missing, biochemical parameters during follow-up were imputed with last observation carried forward. The variation of biochemical parameters and of LSM during OCA therapy was evaluated with linear mixed models. Potential non-linear trajectories were explored by means of restricted cubic splines. When a linear trend was detected (*e.g.* for total bilirubin and LSM), the mean expected change every 12 months was reported from linear mixed models. Conversely, when a non-linear trend over time was evident (*e.g.* for ALP/ULN, ALT/ULN and GGT/ULN), the mean expected change was reported for time intervals based on the observed trajectory. The cumulative incidences of biochemical response and discontinuation of OCA therapy were assessed according to Aalen-Johansen (considering the competing risk of discontinuation) and Kaplan-Meier estimates, respectively. The analyses of factors associated with biochemical response and with occurrence of hepatic AEs were carried out using Cox proportional hazard models and expressed with hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). Multivariable analysis included all variables associated with a *p* value <0.10 in univariate analysis. All analyses were carried out using R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria; <https://www.R-project.org/>).

Results

Characteristics of the study cohort

Sixty-six centres from all over Italy participated to the study. Out of 761 patients with PBC on OCA therapy enrolled from these centres, 747 were included in the final analysis, while two patients were excluded due to incomplete follow-up data (unanswered queries) and 12 patients were excluded due to CP class B/C cirrhosis or a history of previous decompensation. The median follow-up was 24 months (IQR 12-42). Despite the maximum observation period being 54 months, due to the low proportion of patients in follow-up after the 42nd month, response and discontinuation probabilities were censored at 42 months. However, the number and causes of discontinuations occurring after the 42nd month were included in the safety analysis.

The main characteristics of the cohort are shown in Table 1. The average age at the time of PBC diagnosis was in the early fifties, with a predominantly female population. The average age at the start of OCA treatment was in the late fifties. At baseline, the liver biochemical profile showed ALP levels elevated to about twice the ULN and GGT levels elevated to nearly four times the ULN, with normal bilirubin levels. At baseline, pruritus was present in 240 patients (32%). A total of 102 patients (14%) had a diagnosis of AIH/PBC overlap syndrome, histologically confirmed in all cases. All individuals with AIH/PBC overlap syndrome were on stable immunosuppressive therapy for at least 6 months before beginning OCA

Table 1. Main characteristics of the 747 patients on OCA therapy.

Characteristics	n = 747
Demographics and comorbidities	
Sex, female	654 (88%)
Age at PBC diagnosis, years	50.5 (10.9)
Age at OCA start, years	58.3 (10.8)
Duration of disease before OCA start, years	6 (2-12)
BMI*, kg/m ²	24.7 (4.2)
Diabetes mellitus	58 (8%)
Liver disease characterization	
AMA positivity	631 (84%)
ANA positivity	432 (58%)
AIH/PBC overlap syndrome	102 (14%)
Cirrhosis	209 (28%)
Diagnosis of cirrhosis	
Histological	46 (22%)
Elastographic [§]	30 (14%)
Clinical	132 (63%)
Child-Pugh class	
A	209 (100%)
B	- (-%)
C	- (-%)
Oesophageal varices	
Presence	55 (26%)
Gastroscopy not performed	6 (3%)
OCA therapy	
Indication to start OCA	
UDCA intolerance	18 (2%)
Inadequate response	729 (98%) [^]
acc. to Paris I	327 (45%)
acc. to Paris II	685 (96%) ^{^^}
acc. to Toronto	547 (75%)
OCA dose	
5 mg daily	371 (50%)
5 mg daily up-titrated to 10 mg	299 (40%)
OCA mean daily dose	
<5 mg daily	32 (4%)
5 mg daily	413 (55%)
>5 mg daily	302 (40%)
OCA discontinuation	130 (17%)
Time on OCA therapy, months	24 (12-42)
UDCA untreated	18 (2%)
UDCA dose, mg/kg	15 (15-16)
<13 mg/kg/day	79 (11%)
13-15 mg/kg/day	411 (56%)
>15 mg/kg/day	239 (33%)
Concomitant fibrate therapy	104 (14%)
Started before OCA	24 (3%)
Started after OCA	80 (11%)
Time on fibrate therapy during OCA	27 (11-48)
Pruritus at baseline	
History of pruritus	240 (32%)
Pruritus intensity	
Mild	149 (62%)
Moderate	56 (23%)
Severe	22 (9%)
Not reported	13 (5%)
On anti-pruritus therapy	130 (54%)
Biochemistry	
ALP/ULN at baseline	2 (1.7-2.9)
ALT/ULN at baseline	1.1 (0.7-1.6)
AST/ULN at baseline	1.1 (0.8-1.5)
GGT/ULN at baseline	3.9 (2.1-6.3)
Total bilirubin (mg/dl) at baseline	0.7 (0.5-1)
LSM	
N reliable	1,000
LSM per patient	
No LSM	174 (23%)

(continued)

Table 1. (continued)

Characteristics	n = 747
Single LSM	318 (43%)
Serial LSM	255 (34%)
Baseline LSM available	497 (67%)
Baseline LSM, kPa	7.7 (5.9-11.3)
LSM interval, months	12 (12-24)
LSM maximum ≥ 10 kPa	210 (28%)
LSM maximum ≥ 15 kPa	103 (14%)

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; LSM, liver stiffness measurement; OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography. Paris I criteria: ALP $<3\times$ ULN, AST $<2\times$ ULN and bilirubin <1 mg/dl. Paris II criteria: ALP $<1.5\times$ ULN, AST $<1.5\times$ ULN and bilirubin <1 mg/dl. Toronto criteria: ALP $<1.67\times$ ULN.

Data reported as median (IQR) or mean (SD) in case of continuous variables or as numbers with percentages in case of categorical variables.

*Use only for descriptive purposes.

[§]LSM ≥ 16.9 kPa.

[^]98% inadequate responders at OCA prescription, but 96% at OCA start.

^{^^}96% Paris II non-responders at OCA prescription, but 94% at OCA start.

treatment. Concerning the stage of liver disease, 209 patients (28%) had a diagnosis of cirrhosis, and, consistent with exclusion criteria, all of them (100%) had CP class A cirrhosis. Notably, of those with an indication for OCA, the percentage with cirrhosis has nearly halved over time (~40% of those prescribed OCA in 2017-2020 vs. ~20% of those prescribed in 2021-2023; $p < 0.001$) (Table S1).

Most patients received OCA as an add-on therapy due to inadequate response after 12 months of UDCA therapy, while only 18/747 (2%) received it as monotherapy due to intolerance to UDCA. Notably, compared to the time when OCA was prescribed, 26 individuals showed a fluctuation in biochemistry in a subsequent sample taken shortly thereafter and before starting the drug, which classified them as responders according to the Paris II criteria at the time of drug initiation. Moreover, at the time of OCA start, a subgroup of 79 patients (~11%) were underdosed in relation to UDCA treatment (<13 mg/kg/day, with median dose of 12 mg/kg/day, IQR 11-12 mg/kg/day).

A total of 346 patients receiving OCA 5 mg daily did not up-titrate to 10 mg. Of these, 226 were non-responders to the drug at 6 months according to POISE criteria, of whom only 33 and 10 had experienced *de novo* or worsening pruritus, respectively, since the beginning of treatment. Therefore, out of 346 individuals in whom OCA was not up-titrated to 10 mg, 183 (53%) were POISE non-responders without *de novo* or worsening pruritus (missed up-titration). Causes of missed up-titration were not reported.

Approximately 15% of patients were exposed to concomitant fibrate therapy, either starting OCA first and adding fibrates later or starting fibrates first and adding OCA later (Fig. S1). Another 37 patients had previously been exposed to a fibrate, which was discontinued in nine cases at the time of OCA initiation, and in the remaining 28 cases at a median suspension time of 6 months (IQR 2-20 months) before starting OCA.

Effectiveness endpoints

Probabilities of response and trends of hepatic biochemistry in the entire cohort

According to POISE criteria, the probability of response progressively increased from 41% at 12 months to 57% at 42 months. A consistent trend was observed for the probability of

response according to NR criteria, although with much lower percentages (highest response probability: 20% at 42 months) (Fig. 1). The exclusion of patients either not treated with UDCA or underdosed with respect to UDCA (<13 mg/kg) did not change response probabilities (Fig. S2).

Treatment with OCA was associated with a significant reduction in the levels of ALP, ALT, and GGT ($p < 0.001$) (Fig. 2). Notably, a bimodal trend in liver enzymes reduction over time was observed, with a steep drop in the first 12 months and then a much milder decline approaching a plateau. The mean expected drop of liver enzymes in the first 12 months compared to the yearly drop after 12 months was -0.88 (-0.95, -0.82) vs. -0.06 (-0.08, -0.03) for ALP/ULN, -0.55 (-0.63, -0.47) vs. -0.03 (-0.05, -0.012) for ALT/ULN, and -2.92 (-3.15, -2.69) vs. -0.14 (-0.21, -0.07) for GGT/ULN. In contrast, the reduction in total bilirubin levels was lower but still significant over time ($p = 0.02$), with a unimodal (almost flat) trend of variation over time (mean expected drop of total bilirubin -0.01 [-0.02, -0.003] every 12 months) (Fig. 2).

Probabilities of response and trends of hepatic biochemistry in patients with and without cirrhosis

When comparing patients with and without cirrhosis, the response probabilities were significantly lower in those with cirrhosis ($p = 0.02$ for POISE criteria, $p = 0.004$ for NR criteria) (Fig. 3). However, the response in terms of ALP/ULN ($p = 0.41$) and ALT/ULN ($p = 0.71$) reduction did not differ between the two subgroups of patients (Fig. S3). In contrast, significant differences were observed in terms of GGT/ULN and total bilirubin variation under treatment, with a greater mean GGT/ULN drop in patients with cirrhosis compared to those without cirrhosis (every 6 months: -0.40 [-0.45, -0.35] vs. -0.34 [-0.37, -0.31], respectively, $p = 0.04$), and a mild downward trend for total bilirubin in patients without cirrhosis compared to those

with cirrhosis (every 6 months: -0.008 [-0.012, -0.004] vs. 0.003 [-0.007, 0.013], respectively, $p = 0.02$) (Fig. S3).

Probabilities of response and trends in hepatic biochemistry in patients with and without AIH/PBC overlap syndrome

The response rates did not differ when comparing patients with AIH/PBC overlap syndrome and those with pure PBC ($p = 0.8$ for both POISE and NR criteria) (Fig. S4). When considering liver biochemistry parameters over time, there was no difference in response between these two subgroups in terms of ALP ($p = 0.30$), while there were significant differences in terms of ALT, GGT and total bilirubin variation under treatment (Fig. S5). Indeed, a higher mean drop was observed in AIH/PBC overlap syndrome vs. pure PBC for both ALT/ULN (every 6 months: -0.11 [-0.15, -0.08] vs. -0.06 [-0.07, -0.05], respectively, $p < 0.001$) and GGT/ULN (every 6 months: -0.57 [-0.67, -0.46] vs. -0.32 [-0.36, -0.30], respectively, $p < 0.001$), while bilirubin levels showed a slight decline over time in pure PBC but not in AIH/PBC overlap syndrome ($p = 0.02$). Notably, the greater ALT and GGT drop in AIH/PBC overlap syndrome vs. pure PBC was attributable mainly to the first 12 months of treatment (Fig. S5).

Probabilities of response and trends in hepatic biochemistry in patients exposed and those never exposed to triple therapy

The relatively small number in the subgroup of patients on triple therapy with OCA plus a fibrate, coupled with the wide variability in the timing of either OCA initiation after fibrates or fibrates after OCA, preclude any time-dependent analysis that could discern the differential effect of adding a third drug vs. dual therapy. Notably, the exclusion of patients taking concomitant fibrate therapy did not change response probabilities, as shown in Fig. S6. However, the drop over time from baseline in all biochemical parameters was greater in patients exposed in some way to a triple therapy regimen compared to those treated with OCA alone (Fig. S7).

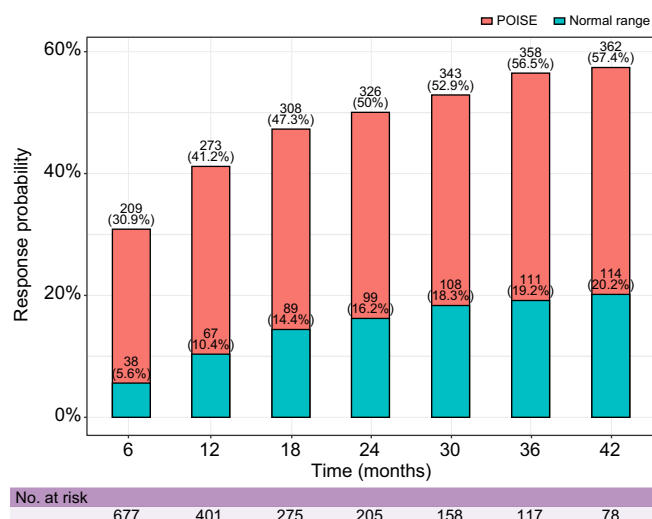


Fig. 1. Probability of response to OCA treatment over time in the overall cohort (n = 747) according to the POISE and the normal range criteria. Numbers over the bars are the cumulative numbers of individuals responding according to POISE/NR criteria along with Aalen-Johansen estimates of the cumulative incidence over time, taking into account the competing risk of OCA discontinuation. NR, normal range; OCA, obeticholic acid.

Safety endpoints

Probabilities of OCA discontinuation in the entire cohort and in relevant subpopulations

The probabilities of discontinuation, in the entire cohort and stratified by the presence/absence of cirrhosis and AIH/PBC overlap syndrome, are shown in Fig. 4A-C. A total of 130 patients (17%) discontinued treatment (Table S2), and the major reasons for discontinuation were pruritus and hepatic AEs (Table S2). The observed hepatic AEs were classified as: i) hepatic decompensation, including the development of ascites, gastro-oesophageal bleeding, and hepatic encephalopathy; ii) worsening of liver function, including the development of jaundice (defined as total bilirubin ≥ 3 mg/dl) and/or cirrhosis CP class progression from A to B/C; and iii) elevation of liver enzymes (at least doubling of AST or ALT and/or ALP) suspected for drug-induced liver injury (DILI). Patients with cirrhosis showed higher discontinuation probabilities compared to those without cirrhosis ($p < 0.001$), while there was no difference between patients with AIH/PBC overlap syndrome and those with pure PBC ($p = 0.06$) (Fig. 4B,C). The discontinuation probability was higher in the first 18 months both in the overall cohort and in the two sub-cohorts stratified for the diagnosis of cirrhosis

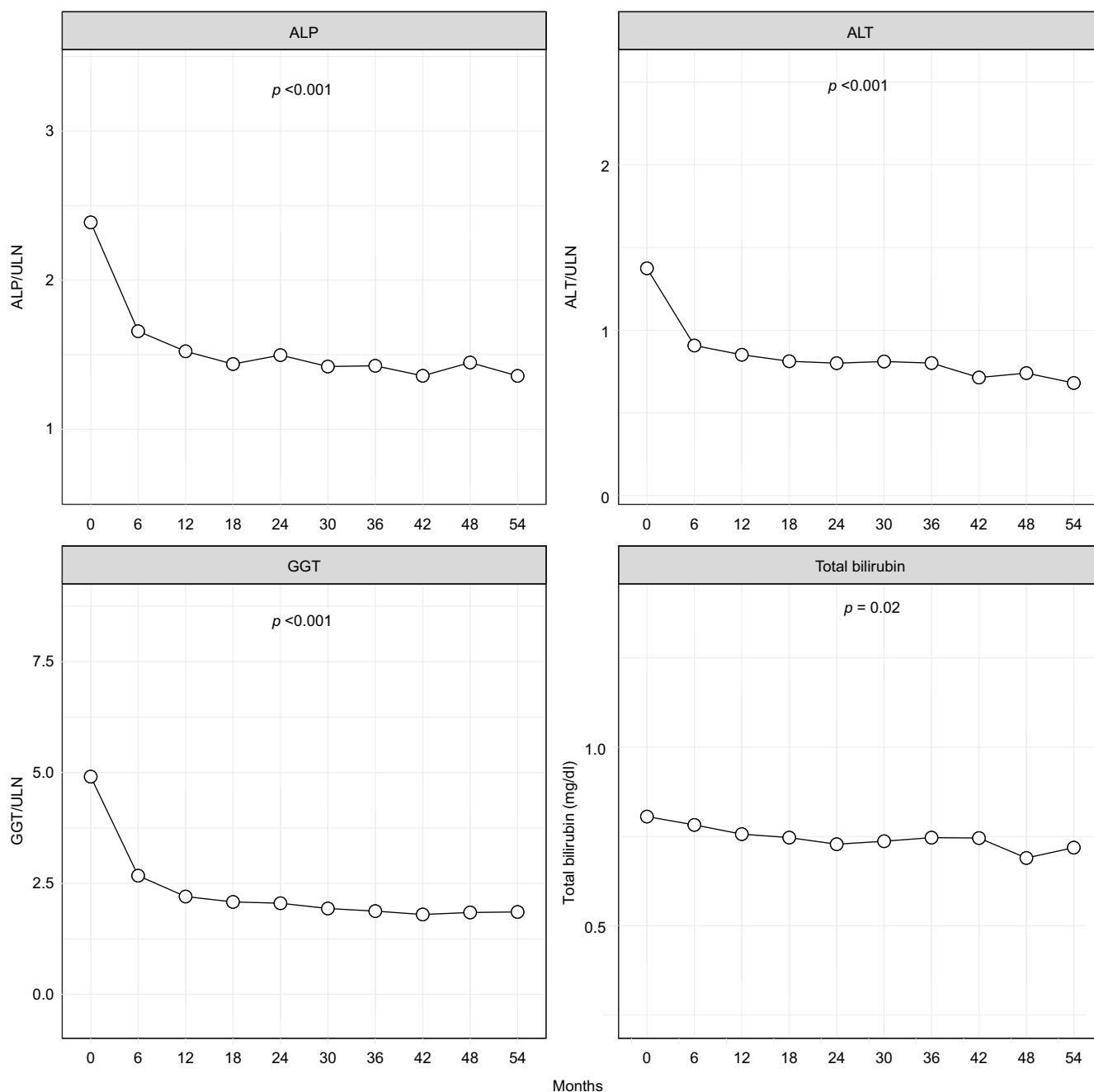


Fig. 2. Variation of liver biochemistry over time (ALP, ALT, GGT, bilirubin). Y-axis values refer to ULN for ALP, ALT, GGT and to mg/dl for total bilirubin. The number over the x-axis represents the number of patients with available measurements. Points and ranges represent mean values $\pm$ SD at each time point. p values for the variation of biochemical parameters over time were estimated with linear mixed models. Levels of significance $p < 0.05$. ALP, alkaline phosphatase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; ULN, upper limit of normal.

(Table S3). Similarly, no differences were observed in the distribution of discontinuations after stratification for the presence/absence of AIH/PBC (Table S4).

Notably, the analysis of the discontinuation causes over time showed a different distribution for pruritus and hepatic AEs ($p = 0.028$) (Table S5). Actually, both pruritus and hepatic AEs occurred more frequently in the first 12 months. However, unlike discontinuations caused by pruritus, those due to hepatic AEs exhibited a bimodal distribution. Indeed, only 4 out of 48

discontinuations due to pruritus (~8%) occurred after the 30th month of treatment compared to 15 out of 37 discontinuations due to hepatic AEs (~37%).

Causes of discontinuation according to the absence/presence of cirrhosis and AIH/PBC and predictors of hepatic AEs

Comparing patients with and without cirrhosis, no significant difference was observed in the probabilities of discontinuation

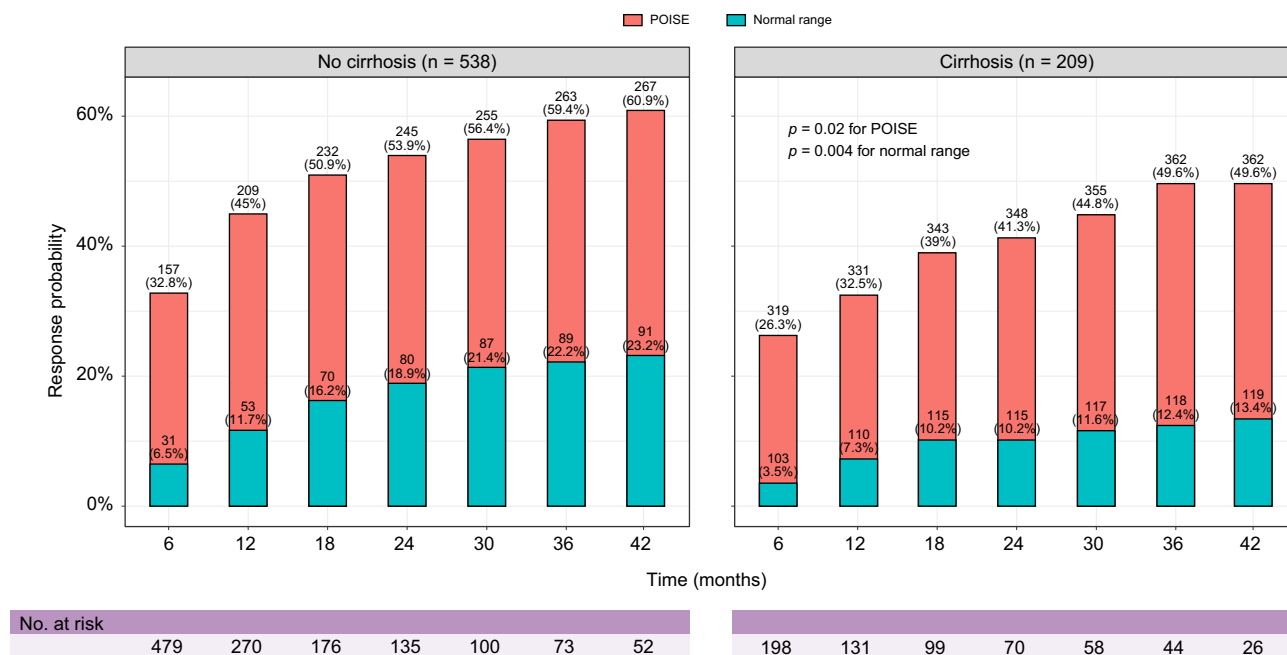


Fig. 3. Probability of response to OCA treatment over time stratified by the presence of cirrhosis. Numbers over the bars are the cumulative numbers of individuals responding according to POISE/NR along with Aalen-Johansen estimates of the cumulative incidence over time, considering the competing risk of OCA discontinuation. Differences of response probabilities between patients with or without cirrhosis were evaluated using the log rank test. Levels of significance $p < 0.05$. OCA, obeticholic acid.

for pruritus ($p = 0.60$) (Fig. S8). In contrast, probabilities of discontinuation for hepatic AEs were significantly higher in patients with cirrhosis ($p < 0.001$) (Fig. S9). Only cirrhosis, baseline bilirubin, LSM at baseline and antinuclear antibody (ANA) positivity were independently associated with the occurrence of hepatic AEs in the multivariate analysis, while the protective effect of response to OCA according to POISE approached statistical significance in the multivariate model (Table S6). Of the 37 hepatic AEs, only three were observed in patients without cirrhosis. Of these, one case was attributed to elevation of liver enzymes (suspected DILI) and two cases to the occurrence of jaundice. The remaining 34 hepatic AEs were observed in patients with cirrhosis. Of these cases, 29 had cirrhosis at baseline (all in CP class A and without a history of decompensation), while five did not have cirrhosis at baseline but had evolved to a diagnosis of cirrhosis at a subsequent time point during follow-up, either before (two cases) or at the time (three cases) of the hepatic AE occurrence. Among the 34 hepatic AEs in patients with cirrhosis: 22 cases were attributed to decompensating events, including eight cases of ascites, nine cases of gastro-oesophageal variceal bleeding, and five cases of hepatic encephalopathy; 12 were attributed to worsening of liver function, including jaundice (eight cases), and/or transition from CP class A to B (three cases) – one with associated development of hepatocellular carcinoma – and from CP class A to C (one case).

LSMs over time during OCA treatment

After the exclusion of unreliable measurements, a total of 1,000 LSMs were captured for the analysis. Baseline LSMs were available in 497 (67%), with a median stiffness of 7.7 kPa (5.9–

11.3). Overall, 573 patients (~77%) had at least one LSM, and 255 had multiple assessments, with a median interval between measurements of 12 months (IQR 12–24).

LSM showed a substantially flat trend over time, with an expected mean annual variation of -0.06 ($-0.31, 0.20$) in the overall cohort (Fig. 5, grey line). However, LSM variation over time significantly differed based on the attainment of biochemical response according to POISE criteria after 1 year of treatment (p for interaction < 0.001) (Fig. 5). Indeed, a mild progressive reduction in LSM was observed in POISE responders (expected mean annual variation -0.48 [$-0.78, -0.19$]) (Fig. 5, green line), while an inverse trend was observed in POISE non-responders (expected mean annual variation 0.33 [$-0.07, 0.73$]) (Fig. 5, red line).

In the analysis of other factors influencing on-treatment variation of LSM, no significant interaction was found for either cirrhosis or overlap AIH/PBC (Table S7). Conversely, the presence of diabetes and baseline liver enzyme levels showed a significant impact on LSM variation under OCA treatment over time (Table S7). Indeed, in the presence of diabetes, LSM variation over time showed an increasing trend, while in the absence of diabetes the trend was decreasing. Similarly, AST or ALT levels $\geq 1 \times$ ULN and ALP or GGT levels $\geq 2 \times$ ULN were associated with an increase in LSM over time, whereas values below these cut-offs were associated with a reduction. The response according to NR criteria, taken individually, did not impact the trend of LSM. This is likely because, within the group of non-responders according to the NR criteria, there were also many who were, however, responders according to the POISE criteria.

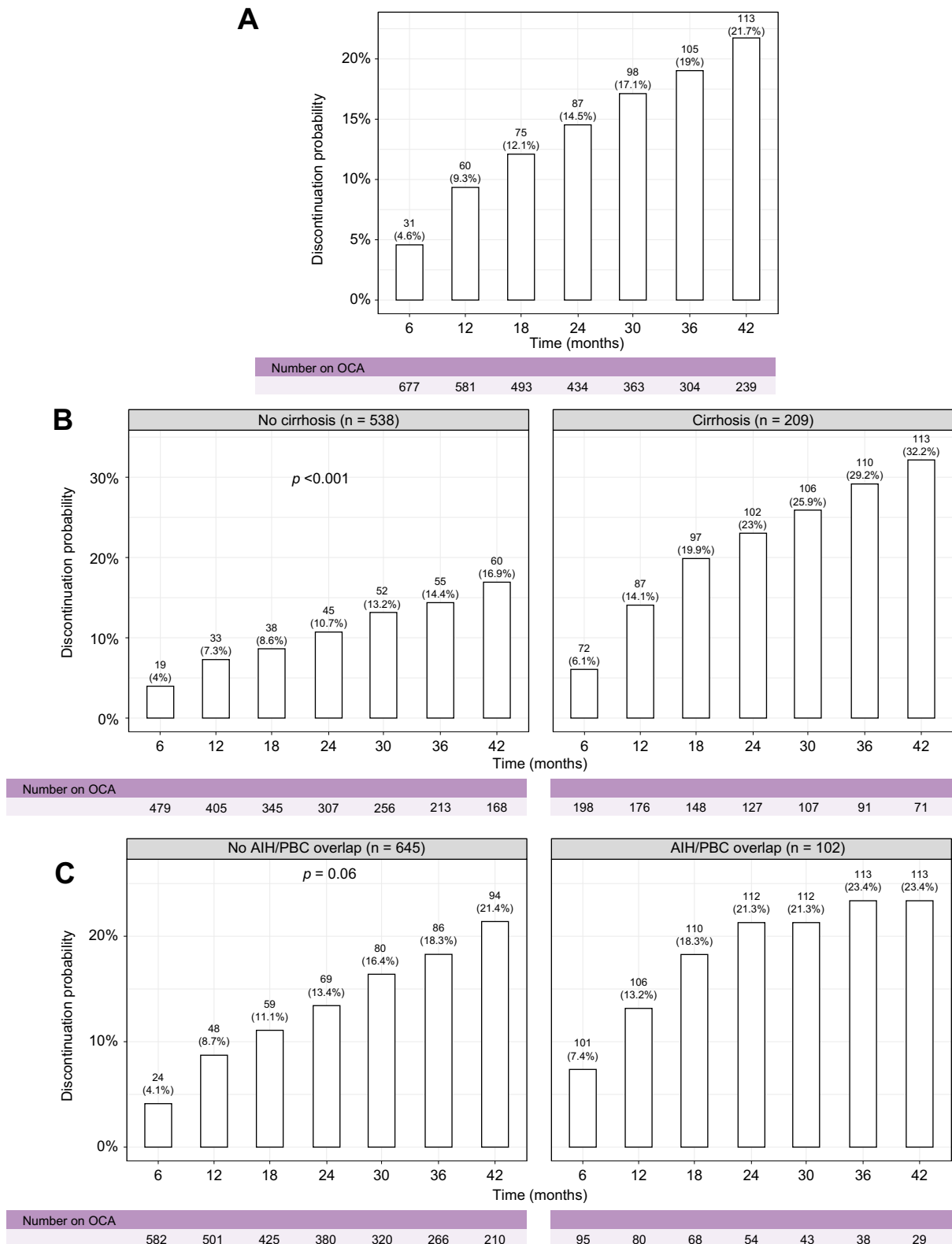


Fig. 4. Discontinuation rates. Discontinuation rate (A) in the entire cohort, (B) by cirrhosis status, and (C) by AIH/PBC overlap status. Numbers over the bars are the cumulative numbers of subjects discontinuing OCA along with Kaplan-Meier estimates of the cumulative incidence over time. Differences of discontinuation probabilities between patients with or without liver cirrhosis and with or without AIH/PBC overlap were evaluated with log rank test. Levels of significance $p < 0.05$. OCA, obeticholic acid; AIH/PBC, autoimmune hepatitis/primary biliary cholangitis.

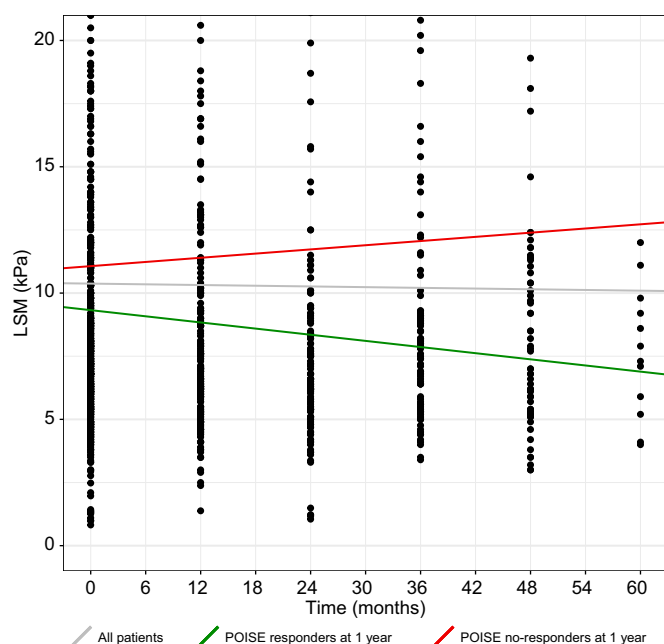


Fig. 5. On-treatment variation of LSM in individuals with PBC treated with OCA in the entire population and divided based on the response to the drug. The variation of LSM over time was evaluated with linear mixed models. A p for interactions was obtained from these models to investigate a differential time trajectory of LSM between patients achieving or not biochemical response. Level of significance $p < 0.05$. LSM, liver stiffness measurement; OCA, obeticholic acid; PBC, primary biliary cholangitis.

Predictors of OCA response

In the univariate analysis, the presence of antimitochondrial antibodies (AMA) and a mean OCA daily dose ≥ 5 mg were positively associated with a biochemical response to OCA therapy according to POISE criteria, while baseline cirrhosis, presence of gastro-oesophageal varices, missed up-titration, presence of pruritus, ALP/ULN, GGT/ULN, and total bilirubin were negatively associated with this endpoint (Table S8). In the multivariate analysis, AMA positivity, mean OCA daily dose ≥ 5 mg, missed up-titration, presence of pruritus, baseline ALP/ULN and total bilirubin were confirmed as independent predictors of response according to POISE criteria (Table S8).

Discussion

Our results, from the largest series of patients with PBC treated with OCA over a medium/long-term follow-up, offer key insights into drug response, pruritus rates, and OCA discontinuation in real-world settings. These data enhance understanding of OCA use in specific groups, including patients with cirrhosis and AIH/PBC overlap syndrome, supporting treatment optimization. Additionally, our findings on LSM trends show that biochemical response correlates with liver necroinflammation and fibrosis improvement, suggesting long-term hepatic benefits. We believe that these results provide valuable insights at a critical moment in the discussion about the risk/benefit profile of OCA in PBC treatment and, more broadly, about the best approach to generating evidence to support the regulatory pathway in rare diseases. Indeed, at present, emerging drugs like PPAR agonists are positioned to fill the unmet need for a second-line therapy in countries where

OCA is no longer available. However, without the support of real-world evidence, these same drugs could face similar regulatory challenges as OCA in the coming years.

Overall, data from our nation-wide, large-scale cohort demonstrate that OCA effectiveness and safety profiles in patients with PBC are maintained in the medium/long term. The probability of response to OCA according to POISE criteria demonstrated a further slight progressive increase after the 12th month to reach a maximum of approximately 57% at 42 months. Since normalisation of liver biochemistry is becoming the new treatment target in PBC,²⁸ response rates according to NR criteria were also evaluated. As expected, the ambitious goal of complete biochemical normalisation was achieved at much lower probabilities, not exceeding 1/5 of the treated patients at the 42nd month.

Consistent with previous studies,^{10,11,14–17} the effect of OCA on liver enzymes was evident from the sixth month after starting treatment, where the most substantial drop compared to baseline was also observed. A clear further decrease in ALP, ALT, and GGT was observed up to the 12th–18th month, while afterwards the decline was much smaller, approaching a plateau. Conversely, bilirubin levels showed a very slight progressive reduction from the beginning of OCA treatment, which, from a clinical standpoint, should be more properly considered a stabilisation.

Notably, 10% of UDCA non-responders were actually undertreated (<13 mg/kg/day). Actually, it is fair to say that the probabilities of OCA response in patients not receiving UDCA or receiving it at subtherapeutic doses did not differ from those receiving UDCA at an adequate dose. Moreover, 50% of patients with an inadequate response to OCA treatment were not up-titrated to 10 mg at the sixth month, despite not experiencing pruritus. We have already demonstrated that up-titration at 6 months leads to a further significant reduction in liver enzymes in these patients.¹⁶ These data should encourage greater recognition of the potential for personalized therapy in patients who may benefit from it.

The probability of OCA discontinuation reached $\sim 20\%$ at 3.5 years, with pruritus as the leading cause, followed by hepatic AEs. While most discontinuations occurred within the first 18 months, a slight increase persisted over time. Late suspensions were mainly due to hepatic AEs, particularly in patients with cirrhosis, as pruritus-related discontinuations were rare after 30 months. Hepatic AEs showed an initial peak and sporadic occurrence later. Since hepatic events are part of the disease's natural history, especially in patients with cirrhosis, it is not possible to determine whether treatment with OCA has a negative, positive, or neutral effect on their development without a control group.

Aside from cirrhosis, the only other factors independently associated with the occurrence of hepatic AEs were baseline total bilirubin, baseline LSM and ANA positivity. Bilirubin is a well-recognised prognostic factor in PBC,²⁶ and we have previously demonstrated a positive association between bilirubin levels and the occurrence of hepatic AEs in patients with PBC-related cirrhosis treated with OCA.²⁹ The findings on LSM are consistently aligned with previous evidence on its predictive capacity for outcomes in patients with PBC.^{27,30} Regarding ANA positivity, our results are consistent with previous observations suggesting a greater disease aggressiveness in patients positive for PBC-specific ANAs, particularly anti-gp210.¹

No differences in the rate and distribution of discontinuations were observed between patients with AIH/PBC overlap syndrome and those with “pure” PBC.

In our cohort, approximately 30% of patients had cirrhosis, all with a preserved liver function (CP class A). In agreement with our previous observation,¹⁶ patients with cirrhosis showed a lower response rate than those without cirrhosis. This finding, rather than indicating a lack of biological activity in this subgroup of patients, was attributable to their higher baseline bilirubin levels and higher discontinuation rate. Indeed, the improvement of liver enzymes (ALP and ALT) was comparable in patients with or without cirrhosis, and the 6-month drop of GGT was even higher in the former. Meanwhile, no significant differences in response and/or treatment tolerance were observed between patients with pure PBC and those with AIH/PBC overlap, in line with what has been reported previously.^{15,16} Our data showed a greater 12-month drop in ALT and GGT in patients with AIH/PBC overlap syndrome compared to those with pure PBC, suggesting either an enhanced effect of OCA on hepatitis secondary to cholestasis or a direct anti-inflammatory/immunomodulatory action.

In the overall cohort, 104 patients had experienced at least one period of triple therapy, most of them receiving fibrates as add-on to UDCA and OCA. In the sensitivity analysis, probabilities of response did not change after excluding these patients. However, individuals on triple therapy showed a greater reduction in liver enzymes, consistent with its known impact on hepatic biochemistry.¹⁹ Unfortunately, the small sample size and variability in the reciprocal initiation of OCA and fibrates limit further insights.

This study is the first to analyse LSM trends during OCA treatment based on drug response. Notably, responders showed LSM reduction, while non-responders experienced an increase, linking biochemical response to improvements in liver necroinflammation and fibrosis. Higher baseline liver enzyme levels, reflecting active inflammation and fibrosis, and diabetes, known for its role in liver damage, both contributed to LSM increases over time. Previous studies highlighted OCA's effect on histological endpoints and fibrosis markers,^{30–32} but data on LSM during therapy remain scarce.^{15,31} As fibrosis stage independently predicts PBC prognosis,³² LSM, the most widely used non-invasive fibrosis test, has proven its value in predicting outcomes.³⁰

From the multivariate analysis, pre-treatment values of ALP and bilirubin, as well as pruritus, were confirmed as negative independent predictors of response to OCA therapy, in line with previous observations in Iberian, UK and Italian cohorts.^{15–17}

Consistently, baseline levels of ALP and bilirubin, as well as pruritus, are among the criteria included in the formula of the OCA response score, which we have recently derived and externally validated to predict the likelihood of response to the drug for individual patients before starting OCA treatment.³³ The direct association between OCA dose and response, along with the inverse link to missed up-titration, underscores the importance of proper drug exposure. Regarding AMA positivity and response likelihood, PBC in the RECAPITULATE cohort followed EASL guidelines, with AMA-negative patients needing specific ANA positivity or diagnostic histology. While exact diagnostic data are missing, many AMA-negative cases likely involved anti-gp210 or anti-sp100 positivity, with anti-gp-210 notably associated with severe bile duct damage and poorer outcomes.¹

This study has limitations. The heterogeneity of the PBC population complicates interpretation of results for specific subgroups, such as those with early or advanced disease. However, the large sample size allowed for representative sub-samples, even after stratification for cirrhosis or AIH/PBC overlap syndrome. Follow-up ended at drug discontinuation, so AEs post-OCA suspension were not captured. A small subgroup of patients considered in the OCA group had been exposed to a fibrate with variable suspension before starting OCA, with a potential residual impact on baseline liver biochemistry. Additionally, the lack of an untreated control group prevents direct comparisons of outcomes with those not receiving second-line therapy, a limitation difficult to overcome in today's real-world context due to OCA and off-label fibrate availability.

This study also has strengths. It is the largest real-world case series described to date on OCA treatment in patients with PBC with a medium/long follow-up. It has collected multiple pieces of information, ranging from how OCA treatment is managed in the real-world context, to the biochemical results that can be expected with this drug and its impact on LSM over time, to the discontinuation rate and the type of events that cause discontinuation.

In conclusion, the results of this extensive Italian real-world cohort of patients with PBC treated with OCA demonstrate that the biochemical response obtained with the drug is substantially maintained in the medium/long term. The probability of OCA discontinuation, mainly due to pruritus or hepatic events, shows a slight progressive increase over time. Moreover, a potential benefit on the trend of LSM over time in those who have a biochemical response to OCA has been observed. The reported data set is very important for understanding and improving OCA treatment in the medium/long term in the context of a rare chronic disease like PBC.

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Abbreviations

AE, adverse event; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; AST, aspartate aminotransferase; COBALT, Clinical Outcomes with Obeticholic Acid in Liver Treatment; CP, Child-Pugh; GGT, gamma-glutamyltransferase; LSM, liver stiffness measurement; NR, normal range; OCA, obeticholic acid; PBC, primary biliary cholangitis; POISE, Primary Biliary Cholangitis Obeticholic acid International Study of Efficacy; ULN, upper limit of normal; UDCA, ursodeoxycholic acid.

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Conflict of interest

Umberto Vespasiani-Gentilucci: consulting fee from Astra Zeneca, Advance Pharma, Ipsen, Novo Nordisk, Mirum, Gilead, Diasorin. Marco Carbone: received consulting fee from Advanz Pharma, Albireo, Ipsen, Cymabay, Gilead, Kowa, Moderna, Echosens, Alphasigma, Genetics SpA, Perspectum, GSK, Mayoly, Zydus. Cristina Rigamonti: Advanz Pharma, Ipsen, Roche.

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Authors' contributions

Study concept and design: UVG, MC, PI, AD, FT. Acquisition of data: all authors and collaborators (see Acknowledgements). Analysis and interpretation of data: UVG, MC, FT, AD. Drafting of the manuscript: UVG, FT, AD, MC. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: AD. Technical or material support: FT, AD. Study supervision: UVG, MC.

Data availability statement

All data of this study are archived in a national PBC registry (the Italian PBC registry) and are available upon reasonable request to the corresponding authors (Umberto Vespasiani-Gentilucci, u.vespasiani@policlinicocampus.it; Marco Carbone, marco.carbone.unimib.it).

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Supplementary data

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