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Effectiveness and safety of obeticholic acid in a Southern European multicenter cohort of patients with primary biliary cholangitis and suboptimal response to ursodeoxycholic acid

Elena Gomez[1] | Luisa Garcia Buey[1] | Esther Molina[2] | Marta Casado[3] | Isabel Conde[4] | Marina Berenguer[4] | Francisco Jorquera[5] | Miguel-Angel Simón[6] | Antonio Olveira[1] | Manuel Hernández-Guerra[7] | Monica Mesquita[8] | Jose Presa[8] | Pedro Costa-Moreira[9] | Guilherme Macedo[9] | Juan I. Arenas[10] | Jose Manuel Sousa[11] | Javier Ampuero[11] | Rosa M. Morillas[12] | Arsenio Santos[13] | Armando De Carvalho[13] | Javier Uriz[14] | Jose A. Carrión[12] | Maria Luisa Gutiérrez[1] | Elia Pérez-Fernández[1] | Conrado M. Fernández-Rodríguez[1] | on behalf of the IBER-PBC leading Cooperative Group

[1]Madrid, Spain
[2]Santiago, Spain
[3]Almeria, Spain
[4]Valencia, Spain
[5]León, Spain
[6]Zaragoza, Spain
[7]Vila Real, Portugal
[8]Porto, Portugal
[9]Santa Cruz de Tenerife, Spain
[10]San Sebastian, Spain
[11]Sevilla, Spain
[12]Barcelona, Spain
[13]Coimbra, Spain
[14]Navarra, Spain

Correspondence
Conrado M. Fernandez-Rodriguez, Gastroenterology Unit, Hospital Universitario Fundacion Alcorcon; Av Budapest-1, 28921-Madrid, Spain.
Email: cfernandez@fhalcorcon.es

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Summary

Background: Obeticholic acid (OCA) was recently approved as the only on-label alternative for patients with primary biliary cholangitis (PBC) with intolerance or suboptimal response to ursodeoxycholic acid (UDCA). However, few data are available outside clinical trials.

Aim: To assess the effectiveness and safety of OCA in a real-world cohort of patients with non-effective UDCA therapy.

Methods: Open-label, prospective, real-world, multicentre study, enrolling consecutive patients who did not meet Paris II criteria, from 18 institutions in Spain and Portugal. Effectiveness was assessed by the changes in GLOBE and UK-PBC scores from baseline. POISE and Paris II criteria were evaluated after 12 months of OCA. Liver fibrosis was evaluated by FIB-4 and AST to platelet ratio index (APRI).

Results: One hundred and twenty patients were eligible, median time since PBC diagnosis 9.3 (4.0-13.8) years, 21.7% had cirrhosis, and 26.7% received had previous or concomitant treatment with fibrates. Seventy-eight patients completed at least 1 year of OCA. The Globe-PBC score decreased to 0.17 (95% CI 0.05 to 0.28; $P = 0.005$) and the UK-PBC score decreased to 0.81 (95% CI −0.19 to 1.80; $P = 0.11$). There was a significant decrease in alkaline phosphatase of 81.3 U/L (95% CI 42.5 to 120; $P < 0.001$), ALT 22.1 U/L (95% CI 10.4 to 33.8; $P < 0.001$) and bilirubin 0.12 mg/dL (95% CI 0 to 0.24; $P = 0.044$). FIB-4 and APRI remained stable. According to the POISE criteria, 29.5% (23 out of 78) achieved response. The adverse events rate was 35%; 11.67% discontinued (8.3% due to pruritus).

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The authors' complete affiliation list are listed in Appendix 1.

Conclusions: This study supports data from phase III trials with significant improvement of PBC-Globe continuous prognostic marker score among OCA-treated patients with good tolerability.

1 | INTRODUCTION

Traditionally, primary biliary cholangitis (PBC) has been considered a rare disease with an important lack of therapeutic options. This chronic, usually slow-progressive, cholestatic liver disease is characterised by the immune-mediated destruction of interlobular bile ducts, thus leading to cholestasis, portal inflammation, fibrosis and, with time and insufficient response to therapy, end-stage liver disease.[1,2] Whereas histologic features help in the disease staging, the key parameters for diagnosis, according to current consensus guidelines, are the co-existence of elevated cholestatic serum biomarkers (serum alkaline phosphatase [AP], gamma-glutamyl-transpeptidase [γ-GT] and bilirubin) and specific anti-mitochondrial antibodies.[3] Liver biopsy is not required for confirming PBC diagnosis, yet this procedure may be needed for AMA-negative and overlap syndromes. Transient elastography (TE) has been increasingly replacing liver biopsy for fibrosis staging. However, this non-invasive procedure has not been extensively validated in PBC as in other chronic liver diseases.[4] In recent years, in order to improve risk stratification, several tools, based on biochemical markers and response to first-line ursodeoxycholic acid (UDCA) therapy[5,6] have been designed and validated to allow the clinical prediction of risk. Moreover, other non-invasive surrogate biomarkers of fibrosis, already validated for other liver diseases, have been extensively used in PBC as prognostic markers.[7,8]

The early identification and close management of patients with PBC, especially now that new therapeutic options are available for those who showed a suboptimal response to UDCA. Fibrates have shown an important impact on AP and bilirubin levels, though no benefit in terms of reversal of fibrosis and/or inflammation has been shown; their use is still off-label for PBC disease, as some safety concerns, specifically its impact on liver transaminases levels still remain.[9] OCA was approved in 2017 in Europe for the therapeutic management of patients with PBC as a second line agent.[10] OCA acts directly on the farnesoid X receptor, showing both in pre-clinical and clinical data a pleiotropic effect on cholestasis, inflammation and liver fibrosis.[10-14] Outside the clinical trial setting, there are very few reports assessing its effectiveness and tolerability in real clinical practice.[15] The aim of this study was to assess the effectiveness and safety of OCA on a real-world patient scenario, of unselected non-responder patients to 12-month UDCA therapy (Paris II criteria).

2 | METHODS

2.1 | Patients and study design

The IBER Leading study group is a scientific consortium of 18 hospitals from Spain and Portugal that has designed this open-label, real practice, prospective study to assess OCA effectiveness and safety among adult patients diagnosed with PBC with a suboptimal response or intolerance to UDCA or disease progression to advanced fibrosis despite adequate biochemical response. Response to OCA was assessed by the continuous prognostic scoring systems GLOBE and UK-PBC.[5,10,16] In addition, dichotomous scores POISE and Paris II criteria were used to evaluate OCA response after at least 12 months of full dose UDCA therapy (13-15 mg/kg/day).[3,17] Eligibility criteria were no response to the Paris II criteria to UDCA or UDCA plus fibrates therapy after at least 1 year of UDCA treatment or the presence of advanced liver fibrosis (F4) even when these patients met the Paris II criteria at baseline. However, the latter did not enter the final analysis (Figure 1).

Patients with overlap syndrome PBC-autoimmune hepatitis as the criteria of Zhang et al[18] were also eligible.

Most enrolled patients (65%) were followed-up for at least 12 months once OCA therapy was initiated. Blood samples were drawn every three months in order to assess the evolution of biochemical, cholestatic and inflammation markers. Patients were categorised in subgroups according to the presence of an optimal response to OCA therapy at the end of the first year of follow-up.

Cirrhosis was diagnosed by liver biopsy (n = 13), TE value ≥ 16.9 kPa (n = 5), and by ultrasound (Nodular liver surface plus splenomegaly or increased diameter of portal vein or ascites or thrombocytopenia $<100 \times 10^9$ platelets) and clinical and biological signs of cirrhosis (n = 8).

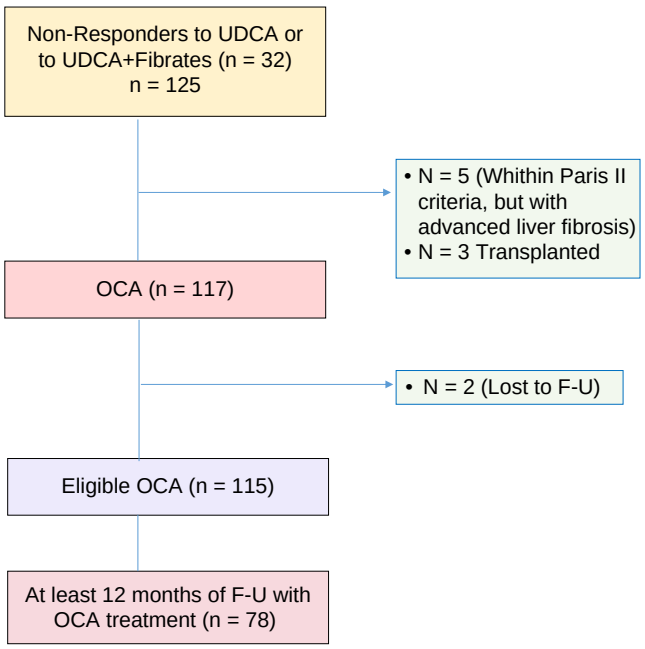

FIGURE 1 Flow chart of patients

Thirty two patients had received fibrates prior to OCA initiation, of these, fibrates were discontinued in ten patients, five due to ineffectiveness and five due to toxicity (four due to increased aminotransferases and one due to worsening of mild renal dysfunction). Two more patients received fibrates after OCA initiation. Therefore, twenty four patients continued receiving fibrates after OCA initiation.

The study was conducted after informed consent according to the principles of the Declaration of Helsinki and approved by the Institutional Research Board of the corresponding centre, and at each participating centre, in accordance with local regulations.

2.2 | End-points

The primary end-point of the study was the effect on the continuous GLOBE and UK-PBC prognostic scores.[5,16] Secondary end-points were the rate of response according to POISE criteria (AP ≤ 1.67 × ULN, with a reduction of at least 15% from baseline, and bilirubin ≤1 mg/dL),[10] the rate of response according to Paris II criteria (ALP ≤ 1.5 × ULN and AST ≤ 1.5 × ULN and bilirubin ≤ 1 mg/dL),[17] the biochemical response to OCA therapy, measured as changes on AP, bilirubin, alanine (ALT) and aspartate aminotransferases (AST), the changes on surrogate markers of fibrosis, such as FIB-4 and AST to platelet ratio index (APRI), after 12 months of therapy and the third end-point was to assess tolerability and safety of the therapy.

2.3 | Clinical parameters

Baseline demographic, clinical, biochemical, histopathological and elastographic parameters were collected for recruited patients, including age, sex, time since PBC diagnosis and UDCA initiation, seropositivity to AMA and ANA antibodies, pruritus or liver fibrosis stage. Baseline was defined as the date OCA therapy was initiated. Each patient enrolled in the study was monitored every 3 months for AP, γ-GT. bilirubin, ALT, AST, total cholesterol, platelets, prothrombin INR, albumin and triglycerides. Additionally, IgM and IgG levels were monitored as surrogate markers of inflammation. Liver fibrosis was also monitored every 3 months by FIB-4 and the APRI parameters, and a liver TE performed by TE (Echosens FibroScan 502) was performed when available at baseline and month 12.

Pruritus was assessed by verbal rating scale, 1 is mild pruritus, 2 moderate and 3 severe, this scale has shown good correlation with visual analogue scales.[19]

2.4 | Statistical analyses

Results were expressed as median and interquartile range for continuous variables and counts and percentages for categorical variables. To observe the effect of treatment on the parameters throughout time, linear mixed models and generalised linear mixed models for repeated measures were used.[17] The time effect was included as repeated measure and adjusted by age. An unstructured variance matrix was considered. The estimated mean differences and 95% confidence intervals (95% CI) are presented. To analyse time effect by response, an interaction effect time × response was added to mixed models. Pairwise comparisons were adjusted using Bonferroni method.

To identify potential predictive factors associated with Paris II optimal response at 12 months, a univariate analysis was performed using the chi-squared test or Fisher's exact test for qualitative variables, and the Mann-Whitney U test for quantitative variables. The variables associated were introduced in multivariate modified Poisson regression model[20,21] to predict Paris II optimal response at 12 months. Receiver operating characteristic (ROC AUC) curves were constructed to evaluate the predictive capacity of parameters and multivariate model linear predictor. The differences were considered statistically significant for $P < 0.05$. The statistical analyses were performed using SPSS software (v. 19.0).

3 | RESULTS

3.1 | Patients characteristics

A total of 125 patients were recruited and 120 of them were eligible. Figure 1 shows the patients' flow chart recruited from 18 Spanish and Portuguese Medical Centres involved in the study, whose baseline characteristics are shown in Table 1. As shown, most patients were female (97%), with a median age of 55.9 (48.2-63) years. Median time since PBC diagnosis was 9.3 (4-13.8) years. Up to 21.7% of the patients enrolled in the study showed cirrhosis at baseline, while 26.7% had received fibrates before the initiation of OCA therapy and 20% received fibrates in combination with UDCA and OCA. Up to 10% of the patients showed an overlap PBC/autoimmune hepatitis syndrome.

There were five patients with advanced fibrosis who met the Paris II criteria at baseline (n = 5), in these patients the median ULNx values of AP was 1.27 (0.94-1.4); Bilirubin 0.61 (0.55-0.8); ALT 1.06 (0.83-1.37) and AST (ULNx) 1.09 (0.9-1.34). At baseline, five patients met Paris II but not Poise criteria. Conversely, there were 14 patients with optimal response to POISE but suboptimal to Paris II Criteria. The criteria for eligibility were lack of response to Paris II criteria after at least 1 year of treatment with UDCA or UDCA plus fibrates.

In 23 AMA-negative patients, diagnosis was confirmed by liver biopsy in 21 cases, the remaining two patients had intrahepatic cholestasis, increased serum IgM and positivity for Anti-GP-210.

3.2 | Continuous Prognostics scores of PBC and surrogate markers of liver fibrosis

UK-PBC decreased to 0.81 (CI95%: −0.19 to 1.8) at 12 months from baseline ($P = 0.11$). The GLOBE score showed significant

TABLE 1 Baseline demographic, clinical and biochemical characteristics of the eligible patients

	N = 120
Age, years (median, IQR)	55.9 (48.2-63.1)
Time since diagnosis, years (median, IQR)	9.3 (4-13.8)
Females (n, %)	116 (96.7)
AMA+ (n, %)	97 (80.8)
ANA + (n, %)	65 (54.2)
Cirrhosis (n, %)	26 (21.7)
CPT A5-A6 (n, %)	20 (80)
CPT B7-B8 (n, %)	5 (20)
Oesophageal varices (n, %)	13 (10.8)
Other autoimmune diseases (n, %)	25 (20.8)
Previous fibrates therapy (n, %)	32 (26.7)
Concomitant fibrates (n, %)	24 (20)
Overlap syndrome (n, %)	12 (10)
Liver biopsy (n, %)	77 (64.2)
Baseline OCA dosage, years (median, IQR)	5 (5-5)
Alkaline phosphatase, U/L (median, IQR)	244 (204-361)
Alkaline Phosphatase × ULN (median, IQR)	2.1 (1.8-2.9)
ALT, U/L (median, IQR)	47 (31-74)
ALT × ULN (median, IQR)	1.4 (0.9-2.1)
AST, U/L (median, IQR)	44 (33-64)
AST × ULN (median, IQR)	1.4 (1-2)
Bilirubin, mg/dL (median, IQR)	0.7 (0.5-1.1)
Bilirubin × ULN (median, IQR)	0.6 (0.5-0.9)
Platelet count, $\times 10^9$ cells/μL (median, IQR)	228.5 (164-300.8)
Platelet count × LLN (median, IQR)	1.4 (0.8-2)
INR (median, IQR)	1 (0.9-1)
Albumin, g/dL (median, IQR)	4.2 (4-4.4)
Albumin × LLN (Median, IQR)	1.2 (1.1-1.3)
IgG, mg/dL (median, IQR)	1315.5 (1142.5-1549.8)
IgM, mg/dL (median, IQR)	335 (226-452)
Cholesterol, mg/dL (median, IQR)	225 (196-260)
Triglycerides, mg/dL (median, IQR)	91 (68-125)
Transient elastography, kPa (median, IQR)	7.9 (6.5-11.3)
MELD (median, IQR)	6 (6-7)
GLOBE-score (median, IQR)	0.3 (−0.4 to 0.9)
PBC globe risk 3 y (median, IQR)	1 (0.9-1)
PBC globe risk 5 y (Median, IQR)	0.9 (0.8-1)
PBC globe risk 10y (median, IQR)	0.8 (0.6-0.9)
PBC globe risk 15y (median, IQR)	0.7 (0.5-0.8)
APRI (median, IQR)	0.6 (0.4-1)
FIB-4 (median, IQR)	1.6 (1.1-2.5)
UK PBC 5y (median, IQR)	2.1 (1.1-3.9)
UK PBC 10y (median, IQR)	6.9 (3.7-12.6)
UK PBC 15y (median, IQR)	12.5 (6.8-22.2)
Follow-up months (median, IQR)	12.3 (6.9-16.9)

improvements up to 0.165 (CI 95%: 0.05-0.28) ($P = 0.005$) (Table 2 and Figure 2).

3.3 | Biochemical changes in markers of cholestasis and inflammation after 12 months of OCA therapy

Seventy-eight patients completed at least 1 year of treatment with OCA. Overall, the biochemical markers assessed along the study period showed statistically significant decrease compared to baseline. The estimated means decrease at 12 months was 81.32 U/L (CI95%: 42.5-120) in AP, 22.1 U/L (CI95%: 10.44-33.77) in ALT, 13.9 (CI95%: 5.34-22.48) in AST and 0.12 (CI95%:0-0.24) in bilirubin (Table 2 and Figure 3). No significant changes were found in IgG levels, however, IgM showed a significant decrease from month 3 after OCA initiation 72.19 mg/dL less at 12 months (CI95%: 28.6-115.77) (Table 2). Total cholesterol decreased to 22.5 mg/dL (CI95%: 8.25-36.78) after 12 months of treatment with OCA (Table 2).

3.4 | Fibrosis evolution with OCA therapy

The surrogate markers of liver fibrosis FIB-4 and APRI did not change throughout the 12 months of OCA treatment. TE results showed that patients experimented a stabilisation of their liver fibrosis throughout this period (Table 2).

3.5 | Factors associated to POISE and Paris II criteria response

Patients treated with OCA were evaluated at the end of the 12 months of follow-up based on both POISE and Paris II criteria. According to the POISE criteria 23 out of 78 patients achieved response (29.5%). The only factor associated to POISE response was serum albumin levels of 4.5 (4.2-4.6) vs 4.2 (4-4.4) ($P = 0.003$; Table 3). Paris II criteria response were achieved by 15 out 78 patients (19.2%). Lower levels of AP (215.0 [198.0-280.0] U/L vs 287 [214.8-402] U/L, $P = 0.005$), total bilirubin (0.5 [0.5-0.8] mg/dL vs 0.8 [0.6-1.1] mg/dL, $P = 0.008$) and triglycerides (123.0 [98.8-191.8] mg/dL vs 88.0 [67-132] mg/dL, $P = 0.012$) at baseline were associated with good response to OCA therapy. These three factors remained independently associated to response at multivariate analysis (Table 4). Serum levels of triglycerides were not correlated with age or the stage of liver fibrosis. A multivariate model was constructed, the ROC AUC for AP, Bilirubin and triglycerides was 0.753, 0.719 and 0.744 respectively, showing good predictive accuracy for Paris II response, the multivariate model linear predictor showed the best ROC AUC 0.877 (CI 95%: 0.79-0.967, Figure S1).

TABLE 2 Adjusted mixed models to evaluate time effect adjusted by age at OCA initiation

Variable	Months	N	Fixed effect time			Pairwise comparisons		
			P-value	Estímate mean	Standard error	Difference from baseline	CI 95%	
Alkaline phosphatase (U/L)	Baseline	116	<0.001[b]	308.45	16.06			
	3	104		252.84	14.58	55.611*	25.94	85.28
	6	99		252.65	14.26	55.804*	24.49	87.12
	12	78		227.13	12.52	81.325*	42.53	120.12
ALT (U/L)	Baseline	116	<0.001[b]	59.53	4.19			
	3	104		46.70	2.94	12.834*	4.83	20.84
	6	100		40.82	2.83	18.709*	7.02	30.40
	12	78		37.43	2.44	22.104*	10.44	33.77
AST (U/L)	Baseline	116	<0.001[b]	52.24	3.32			
	3	104		43.10	2.26	9.141*	2.75	15.53
	6	100		38.88	1.77	13.364*	4.89	21.83
	12	78		38.33	1.69	13.912*	5.34	22.48
TB (mg/dL)	Baseline	115	0.044[a]	0.88	0.06			
	3	104		0.79	0.05	0.095*	0.00	0.19
	6	100		0.78	0.04	0.10	−0.02	0.23
	12	78		0.77	0.05	0.12	−0.01	0.24
IgG (mg/dL)	Baseline	83	0.643	1384.42	38.87			
	3	34		1363.02	48.78	21.40	−79.28	122.08
	6	31		1341.13	38.46	43.29	−51.62	138.20
	12	28		1355.65	38.87	28.78	−56.09	113.65
IgM (mg)	Baseline	81	0.001[a]	383.39	25.86			
	3	35		326.77	22.94	56.626*	13.43	99.82
	6	31		318.35	22.31	65.043*	24.64	105.44
	12	29		311.20	25.51	72.188*	28.60	115.77
Platelet count ($\times 10^9$)	Baseline	115	<0.001[b]	235.44	8.28			
	3	101		223.87	8.38	11.569*	3.00	20.14
	6	98		222.30	8.33	13.140*	2.10	24.18
	12	76		218.31	8.92	17.134*	5.22	29.05
INR	Baseline	111	0.137	1.02	0.03			
	3	90		1.02	0.02	0.00	−0.02	0.02
	6	88		1.03	0.03	−0.01	−0.03	0.02
	12	74		1.04	0.03	−0.02	−0.04	0.01
Albumin (g/dL)	Baseline	111	0.631	4.22	0.03			
	3	90		4.20	0.03	0.02	−0.04	0.09
	6	88		4.19	0.04	0.03	−0.05	0.11
	12	74		4.21	0.04	0.01	−0.07	0.08
Cholesterol (mg/dL)	Baseline	102	0.001[b]	234.34	5.54			
	3	83		219.27	4.62	15.066*	3.37	26.76
	6	84		217.21	5.17	17.126*	3.44	30.81
	12	68		211.82	4.96	22.517*	8.25	36.78
Triglycerides (mg/dL)	Baseline	102	0.301	109.20	6.02			
	3	81		102.26	4.75	6.95	−5.67	19.56

(Continues)

TABLE 2 (Continued)

Variable	Months	N	Fixed effect time *P*-value	Estímate mean	Standard error	Pairwise comparisons Difference from baseline	CI 95%	
	6	82		105.20	5.32	4.00	−7.50	15.49
	12	64		99.05	4.61	10.15	−4.45	24.74
Transient elastography (kPa)	Baseline	85	0.491	13.31	1.35			
	12	39		13.71	1.49	−0.40	−1.56	0.77
MELD	Baseline	92	0.800	6.72	0.14			
	3	77		6.66	0.13	0.06	−0.16	0.28
	6	73		6.70	0.17	0.02	−0.26	0.30
	12	63		6.76	0.18	−0.04	−0.42	0.34
APRI	Baseline	115	0.424	0.84	0.07			
	3	101		0.81	0.08	0.04	−0.10	0.17
	6	98		0.76	0.09	0.09	−0.10	0.28
	12	76		0.76	0.08	0.09	−0.07	0.24
FIB4	Baseline	115	0.235	2.16	0.15			
	3	101		2.21	0.16	−0.05	−0.32	0.21
	6	98		2.23	0.20	−0.07	−0.49	0.34
	12	76		2.34	0.17	−0.18	−0.41	0.05
PBC-GLOBE	Baseline	111	0.005[b]	0.31	0.07			
	12	73		0.14	0.08	0.165[*]	0.05	0.28
UK-PBC5y	Baseline	111	0.110	3.76	0.55			
	12	73		2.95	0.53	0.81	−0.19	1.80

[*] $P < 0.05$.
[a] $P < 0.01$.
[b] $P < 0.01$.

A significant decrease was observed in AP, ALT, AST and bilirubin with OCA treatment in the whole cohort. However, the mixed model detects different trend time in POISE responders vs. non-responders regarding alkaline phosphatase decrease. By contrast, no significant interaction effect time-response was observed in both groups regarding ALT, AST and total bilirubin (Figure S2).

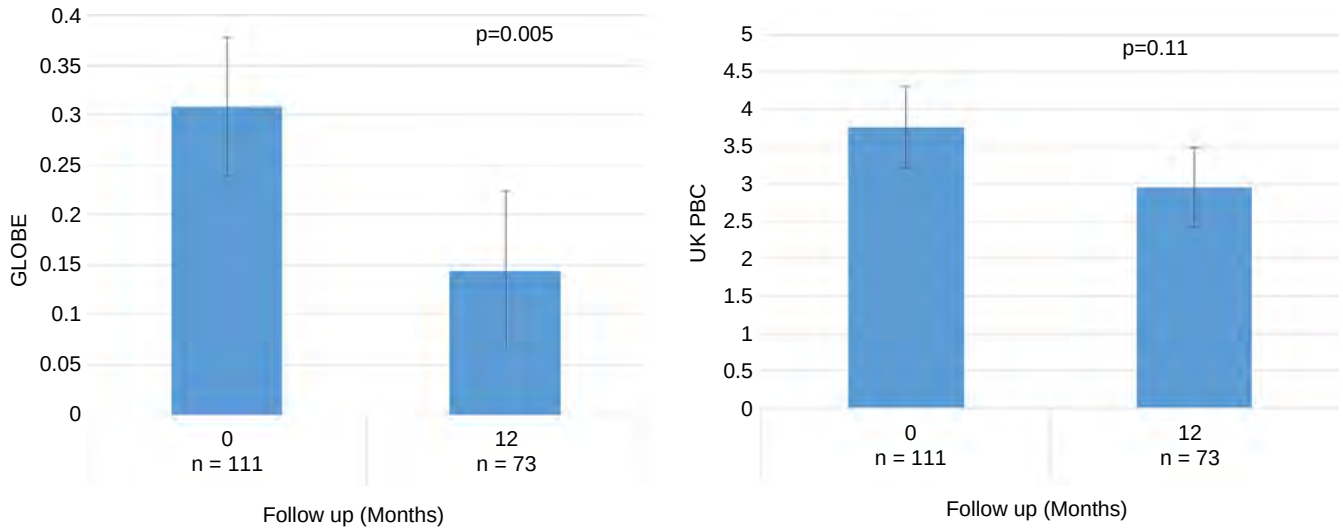

FIGURE 2 OCA effect on continuous outcome scores Globe-PBC and UK-PBC. Mixed models estimated means with standard error bars and *P*-values associated with time effect

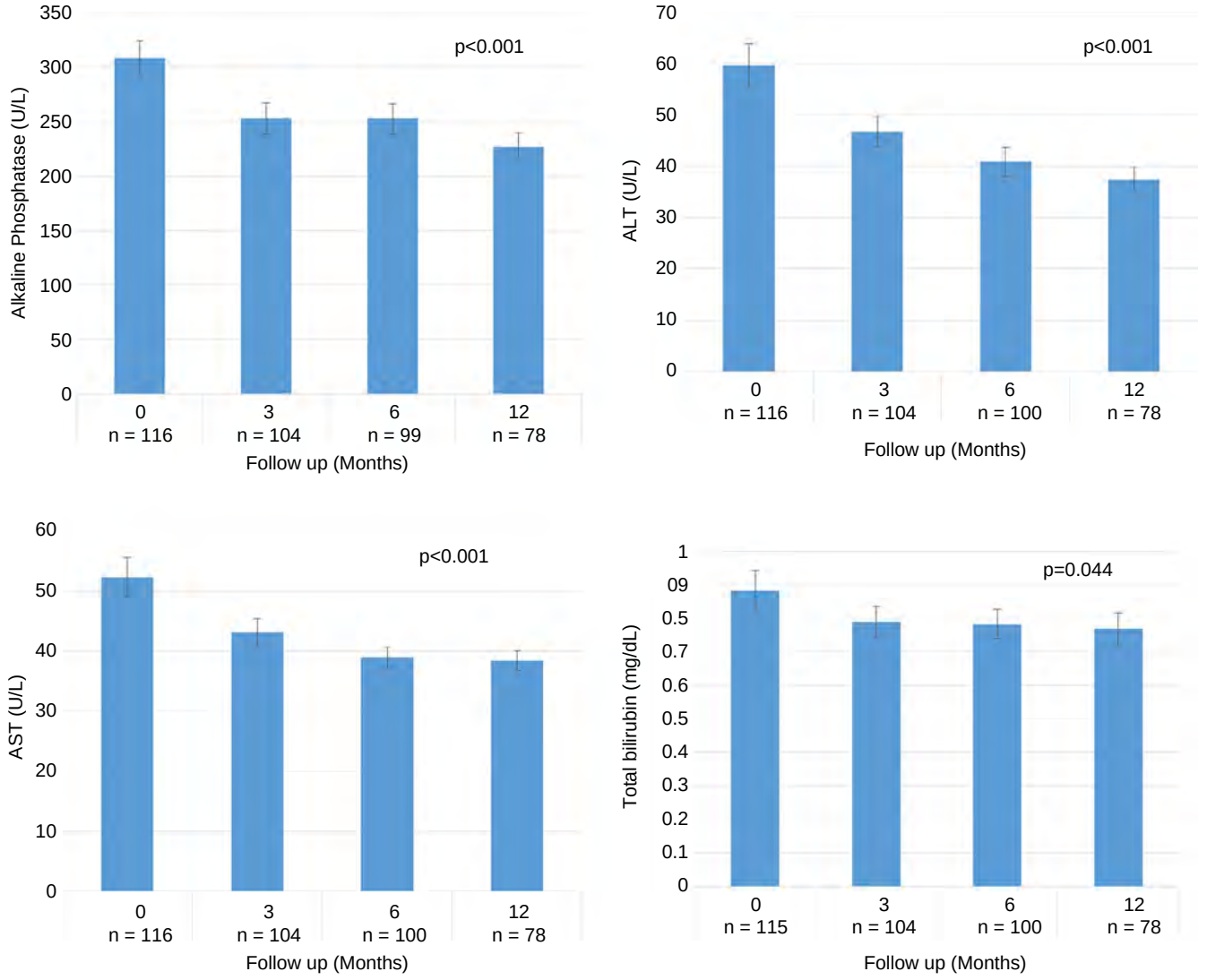

FIGURE 3 Effect of OCA on liver inflammatory and cholestatic serum markers. Mixed models estimated means with standard errors bars and *P*-values associated with time effect

3.6 | Tolerability and safety of OCA therapy

In this study cohort, 35% of the patients showed an episode of adverse event, particularly pruritus (32%). However, 30 patients (24%), experienced grade 1 pruritus at baseline. Eight patients developed liver decompensation during OCA therapy, three of them discontinued and underwent liver transplantation. Ten more cases (8.3%) discontinued due to grade 2-3 pruritus and one more case discontinued due to a flare of cytolysis, this patient had an overlap syndrome PBC-AIH (Table 5).

Pharmacological management of pruritus included cholestyramine (69%), antihistamines (11.9%), bezafibrate (7.1%), naltrexone (4.8%), sertraline (2.4%) and topical calamine oinment, hydratant creams and pramoxine cream (4.8%). In addition, there was a reduction of OCA doses in all cases before definitive withdrawal.

OCA dose was up-titrated to 10 mg in 31 patients, 12 at 6 months and 19 at 12 months.

Seven patients suffered decompensation during OCA treatment, five developed ascites, two patients suffered rupture of oesophageal varices, one of them secondary to pre-sinusoidal portal hypertension associated to nodular regenerative hyperplasia. Three of the patients with ascites underwent liver transplantation. OCA was withdrawn in three patients with ascites, in one patient with overlap PBC/autoimmune hepatitis OCA due to a flare of cytolysis and in 10 cases due to persistent grade 2-3 pruritus (8.3%). Therefore, 14 patients discontinued OCA treatment (11.67%)

In decompensated patients who continued receiving OCA, dosage was adjusted up to 10 mg twice a week in one patient. However, dosage was adjusted up to 5 mg three times a week in four cases of tolerance concerns with a dose of 10 mg twice a week.

4 | DISCUSSION

One third of patients with PBC are non-responders to UDCA and the survival rate in these patients is lower than in the age-and sex-matched healthy population.[22] The management of PBC disease

TABLE 3 Univariate analysis of patients with optimal vs suboptimal response to OCA therapy according to POISE and Paris-II criteria

		POISE response n = 23, 29.5% CI95%: 20.5%-40.4%	POISE No response n = 55	*P*-value	PARISII Optimal n = 15, 19.2% CI 95%:12%-29.3%	PARISII Suboptimal n = 63	*P*-value
Gender	Female	23	55		15	63	
Cirrhosis	No	19 (30.2%)	44 (69.8%)	1	13 (20.6%)	50 (79.4%)	0.722
	Yes	4 (26.7%)	11 (73.3%)		2 (13.3%)	13 (86.7%)	
Cirrhosis	No cirrhosis	19 (30.2%)	44 (69.8%)	0.771	13 (20.6%)	50 (79.4%)	1
	CPT A5-6	4 (33.3%)	8 (66.7%)		2 (16.7%)	10 (83.3%)	
	CPT B7-9		3 (100%)			3 (100%)	
Other autoinmune diseases	No	18 (30.5%)	41 (69.5%)	0.727	10 (16.9%)	49 (83.1%)	0.503
	Yes	5 (26.3%)	14 (73.7%)		5 (26.3%)	14 (73.7%)	
Fibrates	No	15 (26.3%)	42 (73.7%)	0.312	13 (22.8%)	44 (77.2%)	0.331
	Yes	8 (38.1%)	13 (61.9%)		2 (9.5%)	19 (90.5%)	
Concomitant fibrates therapy	No	17 (27.9%)	44 (72.1%)	0.56	13 (21.3%)	48 (78.7%)	0.501
	Yes	6 (35.3%)	11 (64.7%)		2 (11.8%)	15 (88.2%)	
Concomitant treatment	No	13 (33.3%)	26 (66.7%)	0.456	9 (23.1%)	30 (76.9%)	0.389
	Yes	10 (25.6%)	29 (74.4%)		6 (15.4%)	33 (84.6%)	
Overlap	No	19 (27.1%)	51 (72.9%)	0.225	13 (18.6%)	57 (81.4%)	0.646
	Yes	4 (50%)	4 (50%)		2 (25%)	6 (75%)	
Age at OCA therapy start	Median (IQR)	53.2 (46.4-61.4)	57.1 (49.9-64.5)	0.343	59.8 (51.4-62.6)	54.4 (44.9-63.5)	0.358
Years from diagnosis	Median (IQR)	10.9 (5.7-13.8)	11.4 (6.1-14.8)	0.713	11.7 (8.9-18.2)	11 (5.6-14.4)	0.425
Mean doses at baseline	Median (IQR)	5 (5-5)	5 (5-5)	0.15	5 (5-5)	5 (5-5)	0.733
Uptitrated to target dose of 10 mg	No	12 (30.8%)	27 (69.2%)	0.894	8 (20.5%)	31 (79.5%)	0.834
	Yes	10 (32.3%)	21 (67.7%)		7 (22.6%)	24 (77.4%)	
Alkaline phosphatase (U/L)	Median (IQR)	242 (208-303)	279 (209-388)	0.357	215 (198-280)	287 (214-402)	0.005[a]
Alkaline Phosphatase × ULN	Median (IQR)	2.1 (1.9-2.8)	2.4 (2-3.6)	0.308	1.9 (1.6-2.3)	2.4 (2-3.6)	0.003[a]
ALT (U/L)	Median (IQR)	52 (31-74)	42 (27-74)	0.408	52 (29-69)	43 (28-77)	0.944
ALT × ULN	Median (IQR)	1.6 (0.9-2.2)	1.2 (0.8-2.1)	0.417	1.6 (0.9-2)	1.2 (0.8-2.2)	0.834
AST (U/L)	Median (IQR)	36 (31-60)	44 (32-65)	0.580	33 (31-53)	45 (31-71)	0.097
AST × ULN	Median (IQR)	1.1 (0.9-2)	1.4 (0.9-2)	0.788	1.1 (0.9-1.6)	1.4 (0.9-2.2)	0.101
Bilirubin (mg/dL)	Median (IQR)	0.7 (0.5-1)	0.8 (0.5-1.1)	0.449	0.5 (0.5-0.8)	0.8 (0.6-1.1)	0.008[a]
Bilirubin × ULN	Median (IQR)	0.6 (0.5-0.8)	0.7 (0.5-1)	0.463	0.5 (0.4-0.7)	0.7 (0.5-1)	0.008[a]
Bilirubin (mg/dL)	<2	22 (31.9%)	47 (68.1%)	0.268	15 (21.7%)	54 (78.3%)	0.193
	>2	1 (11.1%)	8 (88.9%)			9 (100%)	
Platelet count ($\times 10^9$/L)	Median (IQR)	274 (192-337)	224 (165-311)	0.164	255 (168-285)	231 (183-319)	0.478
Platelet count × LLN	Median (IQR)	1.8 (1.1-2.4)	1.4 (0.8-2.1)	0.245	1.7 (0.8-1.9)	1.5 (1-2.1)	0.474
INR	Median (IQR)	1 (1-1)	1 (0.9-1)	0.071	1 (0.9-1)	1 (0.9-1)	0.463
Albumin (g/dL)	Median (IQR)	4.5 (4.2-4.6)	4.2 (4-4.4)	0.003[a]	4.3 (4.1-4.6)	4.2 (4-4.5)	0.407
Albumin × LLN	Median (IQR)	1.3 (1.2-1.3)	1.2 (1.1-1.3)	0.005[a]	1.2 (1.2-1.3)	1.2 (1.1-1.3)	0.266
IgG (mg/dL)	Median (IQR)	1337 (1140-1803)	1280 (1150-1470)	0.514	1290 (1018.5-1823)	1311 (1145-1516.5)	0.992
IgM (mg/dL)	Median (IQR)	345.5 (247.5-505)	356 (275-478.5)	0.660	380.5 (234.5-775.5)	356 (261.8-464.3)	0.589
Cholesterol (mg/dL)	Median (IQR)	220 (201-243)	234.5 (195.3-269.8)	0.467	209 (192.8-232.5)	235 (201-277)	0.096

(Continues)

TABLE 3 (Continued)

		POISE response n = 23, 29.5% CI95%: 20.5%-40.4%	POISE No response n = 55	*P*-value	PARISII Optimal n = 15, 19.2% CI 95%:12%-29.3%	PARISII Suboptimal n = 63	*P*-value
Triglycerides (mg/Dl)	Median (IQR)	99 (67-136)	88 (70.3-137.5)	0.840	123 (98.8-191.8)	88 (67-132)	0.012[a]
Transient elastography (kPa)	Median (IQR)	8.6 (6.4-10.9)	8.8 (6.3-14.1)	0.684	8.7 (6.6-10.8)	8.6 (6.4-14.2)	0.897
MELD	Median (IQR)	6 (6-6.3)	6 (6-7)	0.221	6 (6-6)	6 (6-7)	0.111
GLOBE	Median (IQR)	0 (−0.4 to 0.4)	0.4 (−0.3 to 1.4)	0.041[a]	-0.1 (−0.6 to 0.5)	0.3 (−0.3-1.2)	0.103
APRI	Median (IQR)	0.6 (0.4-0.7)	0.6 (0.4-1.2)	0.324	0.6 (0.3-0.7)	0.6 (0.4-1.1)	0.329
FIB-4	Median (IQR)	1.2 (0.9-1.8)	1.5 (1.1-2.5)	0.089	1.4 (1.1-1.7)	1.4 (1-2.5)	0.790
UK PBC 5y	Median (IQR)	1.7 (1.2-2.4)	2.4 (1.2-5)	0.152	1.5 (0.8-2.2)	2.2 (1.3-4.8)	0.013[a]

[a]$P < 0.01$.
[b]$P < 0.01$.

TABLE 4 Multivariate modified Poisson regression model. Besides to the three factors found associated to a Paris II response, we introduced age as a recognized factor of response that could also be related to increased triglyceride levels

	Incidence rate ratio	*P*-value	95%CI	
Baseline AP/10 (U/L)	0.914	0.003[a]	0.862	0.970
Baseline BT/0.1 (mg/dL)	0.885	0.011[a]	0.806	0.972
Baseline triglicerydes/10 (mg/dL)	1.083	0.008[a]	1.021	1.150
Age OCA start	0.996	0.891	0.935	1.060

[a]$P < 0.01$.
[b]$P < 0.01$.

TABLE 5 Adverse events among patients treated with OCA

	Total (n = 120)	Cirrhosis (n = 26)
Adverse events (n, %)	42 (35)	6 (23.1)
Serious adverse event (2 with transplantation) (n, %)	8 (7)	3 (11.5)
Discontinuation OCA pruritus (n, %)	10 (8.3)	1 (3.8)
Discontinuation (Cytolytic flare in overlap syndrome PBC-AIH)	1 (0.83)	
Discontinuation due to decompensation (n, %)	3 (2.5)	3 (11.55)
Total discontinuation	14 (11.67)	4 (15.4)
Pruritus (n, %) (30 patients experienced pruritus at baseline)	38 (31.7)	5 (19.2)
Other (n, %)	6 (5)	1 (3.8)
Fatigue (n, %)	4 (3.3)	1 (3.8)
Headache (n, %)	2 (1.7)	
Nausea (n, %)	1 (0.8)	
Nasopharyngitis (n, %)	1 (0.8)	
Arthralgia (n, %)	1 (0.8)	
Decompensation during OCA (n, %)	8 (6.7)	5 (19.2)

has recently evolved with the development of tools to stratify patients based on risk, and the possibility to treat with second line therapy.[23] Recent studies suggest that clinical biochemical parameters together with non-invasive measures of fibrosis can efficiently identify the stage and predict outcomes.[5,24-26] These observations highlight the key importance of monitoring these patients, to identify the stage of the disease on an individual basis, especially now that new therapeutic strategies have emerged.[10] Our results confirm a significant improvement of continuous prognostic risk score GLOBE-PBC, however the improvement in UK-PBC did not reach significance, these results may be due to a relatively low number of patients reaching 1 year of follow-up.[16] There was an improvement of liver biochemical parameters, overall these results in the real-world setting confirm those observed in the POISE trial.[10] While substantial data exist from clinical trials, very scarce information on real-life treatment with OCA is available.[15] The response rate according to the POISE criteria was slightly lower than those observed in the trial.[10] There are several explanations for these results. First, the study population is a priori a hard-to-treat population, not only because of the relatively high percentage of cirrhotic patients (22%) similar to that included in the POISE trial,[10] but also because these are patients who had suboptimal response to UDCA for a long time. In addition, approximately 26.7% of the patients have received OCA as a third line therapy, since they were previously treated with both UDCA plus fibrates. Additionally, over 25% of the patients enrolled in the study were younger than 50 years, which has been associated to worse disease prognosis.[27-29] In addition, OCA therapy may have significant benefit in POISE non-responders as the biochemical inflammatory and bilirubin reduction in POISE non-responders, showed a similar time-trend to POISE responders.

Unlike UDCA or fibrates, OCA has demonstrated choleretic and antifibrotic effects through a putative mechanism of action targeting

the Farneosoid X receptor (FXR). This target is also able to regulate immune response and inflammation, two key counterparts in PBC.[30] Our results point towards these beneficial effects with a reduction in inflammation and immune-modulatory markers, such as IgM, and stabilisation of the stage of fibrosis.

Of note, both PBC-Globe continuous prognostic score significantly improved after 1 year of OCA therapy, this score translates clinical and biochemical parameters into transplant-free survival.[5,16]

We speculated that the platelet count decline could be due to an anti-inflammatory effect of OCA. This decrease has been previously described in patients with cirrhosis,[15] the authors claimed a note of caution with OCA dose in these patients. However, we did not see any difference in the platelet count reduction with cirrhosis ($P = 0.364$) or with age ≥ 60 or <60 years old ($P = 0.672$). In any case, the decline was small and clinically not relevant. This platelet count reduction may have prevented a significant decrease in APRI and FIB-4 scores as the platelet count is part of the denominator of these surrogate markers of liver fibrosis.

The higher levels of serum albumin were associated to higher response rate to POISE criteria, it may reflect that treatment initiation in early stages of liver disease increases the likelihood of response to OCA therapy.[31]

The lower rate of Paris II response in patients with lower levels of triglycerides was not associated with younger age or with higher stages of liver fibrosis. We speculate that low fasting triglyceride levels may be associated to higher stages of liver fibrosis. In this regard, a recent large American population-based study has showed an inverse relationship between liver fibrosis indicators and fasting serum triglycerides.[32]

Regarding the tolerability and safety of the OCA therapy in this cohort, it is worthy to note that pruritus remains the main adverse event, though a great proportion of the patients already had it at baseline, and only nine patients experienced pruritus on a de novo basis after the initiation of OCA. This relatively low rate of patients experiencing pruritus with OCA may be related with the high proportion of patients with the dose of 5 mg.[13] Although the exact mechanism of this cholestatic pruritus remains to be elucidated, two hypotheses have arisen: the activation of the autotaxin pathway[33] or the activation of TGR5,[34,35] another target of OCA.[36] Paradoxically, OCA activation of TGR5 improves ethanol-induced liver injury in murine models.[37]

In conclusion, we present this observational study of real-world clinical practice assessing the efficacy and tolerability of OCA in a hard-to-treat cohort of patients with PBC. Most patients benefitted from the treatment with OCA in terms of improvement of Globe-PBC scoring system, and about one third achieved the POISE criteria at the end of the first 12 months of therapy, considering the hard-to-treat profile of patients enrolled in the study. In addition, those who did not achieve these criteria showed significant improvements of some biochemical parameters. Further studies and longer follow-up would be needed to identify whether this population can be considered as slow responders instead of non-responders. Moreover, an improvement in immunomodulatory markers and stabilisation of fibrosis progression was noted. Finally, OCA did not induce unexpected adverse events.

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AUTHORSHIP

Guarantor of the article: Conrado M Fernandez-Rodriguez

Author contributions: All co-authors contributed to the study design, gathering data and approved the final version of the manuscript. Elia Perez-Fernandez undertook the statistical analysis.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Javier Ampuero https://orcid.org/0000-0002-8332-2122
Conrado M. Fernández-Rodríguez https://orcid.org/0000-0002-1915-2157

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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APPENDIX 1

The authors complete affiliation details.

Elena Gomez, Hospital Universitario 12 de Octubre, Madrid, Spain; Luisa Garcia Buey, Hospital Universitario de La Princesa, Madrid, Spain; Marta Casado, Complexo Hospitalario Universitario de Santiago, Santiago de Compostela, A Coruña, Santiago, Spain; Isabel Conde and Marina Berenguer, Hospital Universitario Torrecárdenas, Almeria, Spain; Francisco Jorquera, Hospital Universitario La Fe; Ciberehd, Valencia, Spain; Miguel-Angel Simón, Complejo Asistencial Universitario de León Ciberehd, León, Spain; Antonio Olveira, Hospital Universitario Lozano Blesa, Zaragoza, Spain; Manuel Hernández-Guerra, Hospital Universitario La Paz, Madrid, Spain; Monica Mesquita, Centro Hospitalar de Trás-Os-Montes e Alto Douro, Vila Real, Portugal; Jose Presa, Centro Hospitalar São João, Porto, Portugal; Pedro Costa-Moreira and Guilherme Macedo, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; Juan I. Arenas, Hospital Universitario Donostia, San Sebastian, Spain; Jose Manuel Sousa, Hospital Virgen del Rocío Ciberehd, Sevilla, Spain; Javier Ampuero, Hospital Germans Trias i Pujol, Barcelona, Spain; Arsenio Santos and Armando De Carvalho, Centro Hospitalar Universitário de Coimbra, Coimbra, Spain; Javier Uriz, Complejo Hospitalario de Navarra, Navarra, Spain; Jose A. Carrión, Hospital del Mar, Barcelona, Spain; Maria Luisa Gutiérrez, Elia Pérez-Fernández and Conrado M. Fernández-Rodríguez, Hospital Universitario Fundación Alcorcón, Madrid, Spain.