Real-world experience with obeticholic acid in patients with primary biliary cholangitis

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Table of contents

Supplementary methods

Indications to OCA treatment

Indications to OCA treatment, which in Italy essentially coincides with the criteria by which second-line therapy with OCA is reimbursed by the National Health Service, are an ALP≥1.5 per upper limit of normal (ULN) and/or 1mg/dL≤bilirubin≤2mg/dL after at least 12 months of treatment with UDCA, or the intolerance to UDCA. According to the package insert in Italy, in patients with compensated cirrhosis, OCA therapy should be initiated at 5 mg/day dose and re-evaluated after six months for possible up-titration at 10 mg/day in case of suboptimal response, where suboptimal response is not further defined but generally assumed to be an ALP level still ≥1·5/UNL. Conversely, in patients with decompensated liver disease (Child-Pugh B and C cirrhosis), OCA is recommended to be started at 5 mg/week dose, and, if tolerated and judged necessary according to suboptimal response after three months, gradually up-titrated until a maximum dose of 10 mg twice weekly.

Supplementary results

Table S1. Characteristics of study population according to the presence of cirrhosis

Characteristic	Liver Cirrhosis		p-value
	No, N = 130	**Yes**, N = 61	
Sex, female	120 (92%)	60 (98%)	0·2
Age at diagnosis, years	48 (40, 55)	50 (42, 56)	0·2
Age at OCA start	56 (47, 62)	61 (53, 66)	0·003
AIH Overlap	17 (13%)	11 (18%)	0·5
Centre level			0·6
Secondary	66 (51%)	28 (46%)	
Tertiary	64 (49%)	33 (54%)	
UDCA dose, mg/kg	15·0 (15·0, 17·0)	15·5 (15·0, 18·0)	0·4
Duration of disease before OCA start, years	6·0 (3·0, 11·0)	8·0 (5·0, 13·0)	0·086
OCA dose			<0·001
< 5 mg daily	3 (2·3%)	7 (11%)	
5 mg daily	69 (53%)	46 (75%)	
5 mg up-titrated to 10 mg daily	58 (45%)	8 (13%)	
ALP/ULN at baseline	2·06 (1·61, 2·72)	2·18 (1·73, 3·06)	0·2
ALT/ULN at baseline	1·21 (0·74, 1·75)	1·10 (0·82, 1·89)	0·7
AST/ULN at baseline	1·00 (0·74, 1·40)	1·23 (1·00, 2·17)	<0·001
GGT/ULN at baseline	4·0 (2·4, 6·9)	4·6 (2·8, 7·4)	0·4
Total Bilirubin/ULN at baseline	0·70 (0·50, 1·00)	1·00 (0·70, 1·30)	<0·001
ALP/ULN at 12 months	1·38 (1·09, 1·80)	1·34 (1·12, 1·80)	0·6
AST/ULN at 12 months	0·83 (0·65, 1·00)	0·97 (0·73, 1·19)	0·018
ALT/ULN at 12 months	0·85 (0·54, 1·08)	0·78 (0·50, 1·04)	0·7
GGT/ULN at 12 months	1·45 (0·90, 2·85)	1·91 (1·04, 3·01)	0·7
Total Bilirubin at 12 months	0·56 (0·40, 0·88)	0·91 (0·57, 1·07)	<0·001
Bilirubin Delta at 12 months	-14 (-30, 9)	-4 (-21, 12)	0·2
OCA started after Fibrates	4 (3·1%)	2 (3·3%)	>0·9
OCA discontinuation before 12 m	15 (12%)	18 (30%)	0·004
Reason for OCA discontinuation			0·11
Abdominal pain	1 (4·8%)	1 (5·0%)	
Anaemia	0 (0%)	2 (10%)	
Death for TIPS complications	0 (0%)	1 (5·0%)	
Demyelinating disease	1 (4·8%)	0 (0%)	
Dizzying syndrome	1 (4·8%)	0 (0%)	
Eczema	0 (0%)	1 (5·0%)	
Headache	0 (0%)	1 (5·0%)	
Myalgia	1 (4·8%)	0 (0%)	
OCA intolerance	1 (4·8%)	0 (0%)	
Pruritus	15 (71%)	11 (55%)	
Worsening liver enzymes	1 (4·8%)	0 (0%)	
Worsening liver function	0 (0%)	3 (15%)	

Data expressed as median (interquartile range) or number (percentage).
Comparisons carried out with χ^2 test or Mann-Whitney U test as appropriate.

Table S2. Characteristics of study population according to presence of PBC-AIH overlap

Characteristic	PBC-AIH overlap		p-value
	No, N = 163	**Yes**, N = 28	
Sex, female	152 (93%)	28 (100%)	0·4
Age at diagnosis, years	49 (42, 56)	44 (38, 51)	0·015
Age at OCA start	58 (49, 65)	54 (45, 58)	0·011
Cirrhosis	50 (31%)	11 (39%)	0·5
Centre level			0·080
Secondary	85 (52%)	9 (32%)	
Tertiary	78 (48%)	19 (68%)	
UDCA dose, mg/kg	15·0 (15·0, 17·0)	16·3 (15·0, 20·2)	0·019
Duration of disease before OCA start, years	7·0 (3·0, 11·0)	6·0 (3·8, 11·2)	0·6
OCA dose			0·2
< 5 mg daily	9 (5·5%)	1 (3·6%)	
5 mg daily	102 (63%)	13 (46%)	
5 mg up-titrated to 10 mg daily	52 (32%)	14 (50%)	
ALP/ULN at baseline	2·07 (1·68, 2·70)	2·13 (1·73, 3·47)	0·4
ALT/ULN at baseline	1·06 (0·75, 1·74)	1·66 (1·22, 2·37)	0·003
AST/ULN at baseline	1·05 (0·79, 1·46)	1·29 (0·99, 2·13)	0·048
GGT/ULN at baseline	4·0 (2·3, 6·3)	6·2 (3·1, 12·3)	0·033
Total Bilirubin/ULN at baseline	0·80 (0·59, 1·00)	0·79 (0·53, 1·11)	0·8
ALP/ULN at 12 months	1·36 (1·08, 1·80)	1·35 (1·10, 1·76)	>0·9
AST/ULN at 12 months	0·80 (0·65, 1·00)	1·00 (0·91, 1·32)	0·003
ALT/ULN at 12 months	0·76 (0·50, 1·03)	0·94 (0·78, 1·20)	0·028
GGT/ULN at 12 months	1·42 (0·92, 2·62)	2·54 (1·00, 3·60)	0·047
Total Bilirubin at 12 months	0·60 (0·44, 0·90)	0·80 (0·40, 1·00)	0·4
Bilirubin Delta at 12 months	-11 (-28, 9)	-10 (-27, 15)	0·9
OCA started after Fibrates	4 (2·5%)	2 (7·1%)	0·2
OCA discontinuation before 12 m	30 (18%)	3 (11%)	0·4
Reason for OCA discontinuation			0·4
Abdominal pain	2 (5·7%)	0 (0%)	
Anaemia	2 (5·7%)	0 (0%)	
Death for TIPS complications	1 (2·9%)	0 (0%)	
Demyelinating disease	0 (0%)	1 (17%)	
Dizzying syndrome	1 (2·9%)	0 (0%)	
Eczema	0 (0%)	1 (17%)	
Headache	1 (2·9%)	0 (0%)	
Myalgia	1 (2·9%)	0 (0%)	
OCA intolerance	1 (2·9%)	0 (0%)	
Pruritus	22 (63%)	4 (67%)	
Worsening liver enzymes	1 (2·9%)	0 (0%)	
Worsening liver function	3 (8·6%)	0 (0%)	

Data expressed as median (interquartile range) or number (percentage).
Comparisons carried out with $\chi 2$ test or Mann-Whitney U test as appropriate.

Table S3. Characteristics of study population according to Secondary and Tertiary centers.

Characteristic	Centre level		p-value
	Secondary, N = 94	**Tertiary**, N = 97	
Sex, female	90 (96%)	90 (93%)	0·6
Age at diagnosis, years	51 (42, 57)	47 (40, 54)	0·027
Age at OCA start	59 (53, 64)	54 (47, 63)	0·018
AIH Overlap	9 (9·6%)	19 (20%)	0·080
Cirrhosis	28 (30%)	33 (34%)	0·6
UDCA dose, mg/kg	15·0 (15·0, 16·9)	15·1 (15·0, 18·0)	0·2
Duration of disease before OCA start, years	7·0 (4·0, 11·8)	6·0 (3·0, 11·0)	0·4
OCA dose			0·079
< 5 mg daily	8 (8·5%)	2 (2·1%)	
5 mg daily	58 (62%)	57 (59%)	
5 mg up-titrated to 10 mg daily	28 (30%)	38 (39%)	
ALP/ULN at baseline	2·05 (1·66, 2·66)	2·13 (1·74, 3·16)	0·10
ALT/ULN at baseline	1·06 (0·80, 1·70)	1·27 (0·77, 1·91)	0·2
AST/ULN at baseline	1·06 (0·77, 1·47)	1·06 (0·86, 1·70)	0·5
GGT/ULN at baseline	3·5 (1·9, 6·0)	4·7 (2·8, 8·9)	0·004
Total Bilirubin/ULN at baseline	0·90 (0·60, 1·10)	0·73 (0·51, 1·00)	0·3
ALP/ULN at 12 months	1·26 (1·02, 1·53)	1·50 (1·13, 2·03)	0·004
AST/ULN at 12 months	0·77 (0·65, 1·00)	0·91 (0·70, 1·10)	0·057
ALT/ULN at 12 months	0·70 (0·49, 0·92)	1·00 (0·57, 1·15)	0·002
GGT/ULN at 12 months	1·12 (0·75, 2·19)	2·17 (1·20, 3·58)	<0·001
Total Bilirubin at 12 months	0·65 (0·45, 1·00)	0·59 (0·42, 0·92)	0·6
Bilirubin Delta at 12 months	-10 (-24, 10)	-14 (-29, 9)	0·5
OCA started after Fibrates	0 (0%)	6 (6·2%)	0·029
OCA discontinuation before 12 m	19 (20%)	14 (14%)	0·4
Reason for OCA discontinuation			0·8
Abdominal pain	1 (4·8%)	1 (5·0%)	
Anaemia	0 (0%)	2 (10%)	
Death for TIPS complications	1 (4·8%)	0 (0%)	
Demyelinating disease	1 (4·8%)	0 (0%)	
Dizzying syndrome	1 (4·8%)	0 (0%)	
Eczema	0 (0%)	1 (5·0%)	
Headache	1 (4·8%)	0 (0%)	
Myalgia	0 (0%)	1 (5·0%)	
OCA intolerance	0 (0%)	1 (5·0%)	
Pruritus	13 (62%)	13 (65%)	
Worsening liver enzymes	1 (4·8%)	0 (0%)	
Worsening liver function	2 (9·5%)	1 (5·0%)	

Data expressed as median (interquartile range) or number (percentage).
Comparisons carried out with $\chi 2$ test or Mann-Whitney U test as appropriate.

Table S4. Factors associated with lack of response to obeticholic acid at 6 months.

	Univariate	Multivariate	
Variable	**RR (95%CI), p**	**aRR (95%CI), p**	**aRR* (95%CI), p**
Age, years	1.00 (1.00-1.01), 0.332		
Age at PBC diagnosis, years	1.01 (0.99-1.02), 0.333		
Age at OCA start, years	1.00 (1.00-1.01), 0.335	1.01 (1.00-1.03), 0.068	1.01 (1.00-1.02), 0.131
Male sex	1.26 (0.93-1.70), 0.131	0.75 (0.40-1.41), 0.374	0.71 (0.37-1.35), 0.296
ANA positivity	0.86 (0.68-1.09), 0.226		
AMA positivity	0.91 (0.70-1.18), 0.479		
Liver cirrhosis	1.18 (0.97-1.45), 0.099	1.23 (0.95-1.58), 0.114	1.18 (0.92-1.53), 0.199
PBC-AIH overlap	0.97 (0.72-1.31), 0.842		
Triple therapy with UDCA, OCA & Fibrates	1.09 (0.67-1.76), 0.736		
OCA started after Fibrates	1.27 (0.88-1.85), 0.203		
Duration of PBC, years	1.00 (0.98-1.01), 0.692		
ALP/ULN at baseline	1.07 (1.00-1.14), 0.043	1.14 (1.04-1.25), 0.004	1.13 (1.03-1.24), 0.009
ALT/ULN at baseline	1.10 (1.02-1.18), 0.011	1.00 (0.82-1.23), 0.963	1.02 (0.83-1.25), 0.853
AST/ULN at baseline	1.12 (1.03-1.21), 0.006	0.95 (0.78-1.17), 0.640	0.92 (0.75-1.12), 0.402
GGT/ULN at baseline	1.01 (1.00-1.03), 0.034	1.00 (0.98-1.02), 0.759	1.01 (0.99-1.03), 0.435
Total bilirubin/ULN at baseline	1.15 (1.04-1.28), 0.007	1.17 (1-1.37), 0.046	1.14 (0.97-1.33), 0.113

Response to OCA evaluated according to Poise criteria in the intention-to-treat population.

Abbreviations: aRR, adjusted risk ratio; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine-transferase; AST, aspartate-transferase; AMA, anti-mitocondrial antibodies; ANA, antinuclear antibodies; CI, confidence intervals; GGT, gamma-glutamyl transferase; OCA, obeticholic acid; PBC, primary biliary cholangitis; RR, risk ratio; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

* additionally corrected for OCA discontinuation.

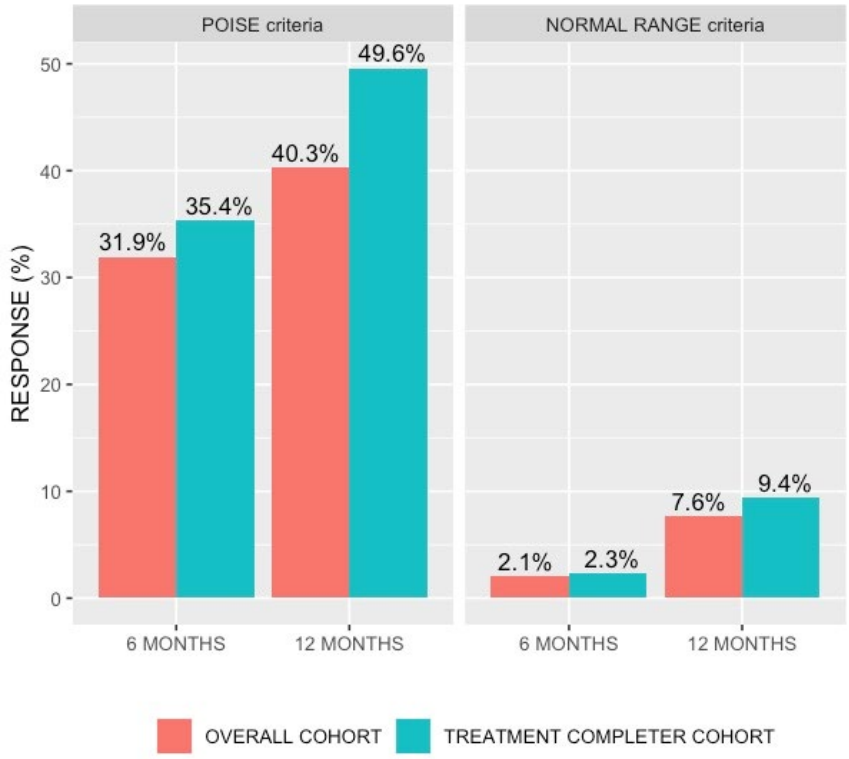

Fig. S1. Rates of response to OCA therapy according to the POISE (left panel) and the normal range criteria (right panel) in the 144 patients with ALP/UNL ≥ 1.67, of the Overall cohort and treatment completers cohort.

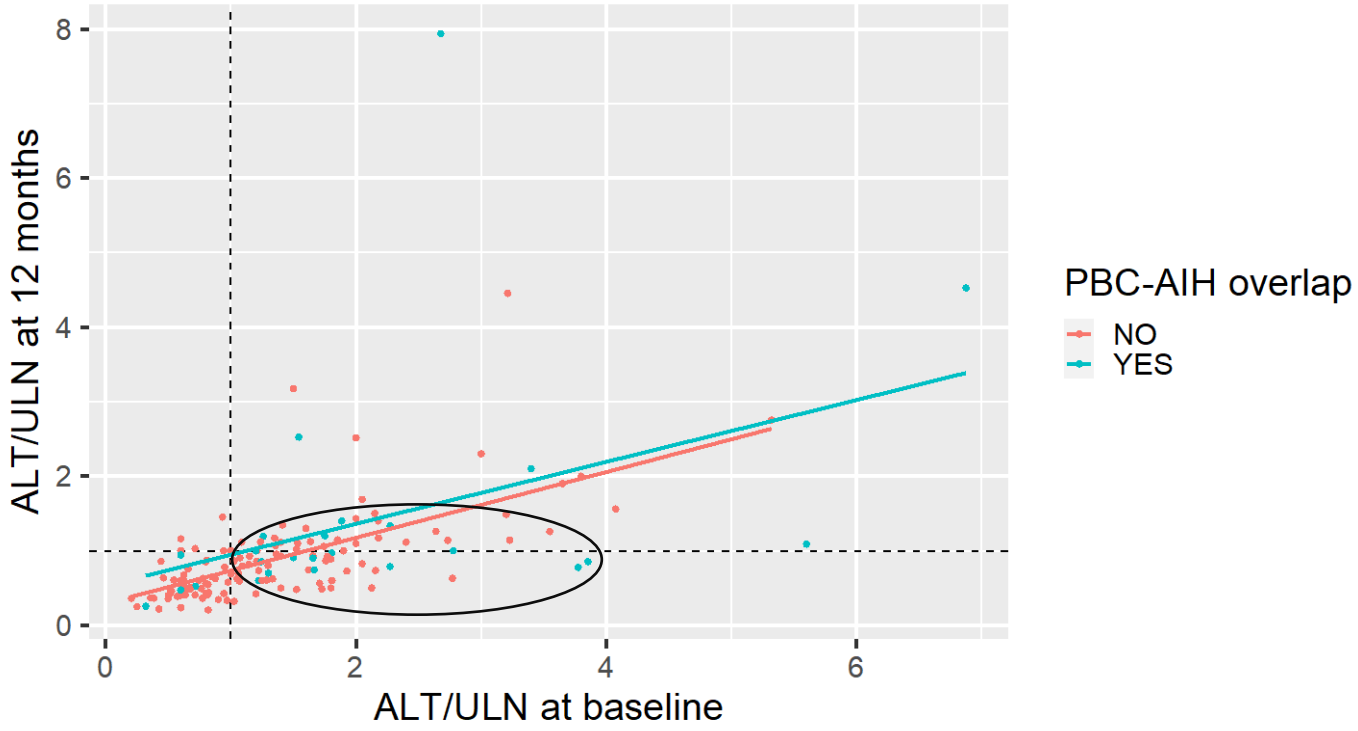

Fig. S2. Improvement of ALT/ULN levels after 12 months of treatment with OCA in patients with pure PBC and AIH-PBC overlap.

Safety and side effects

Assessment of safety and side effects included adverse events, laboratory variables, and systematic assessment of pruritus.

Within the study period four patients experienced serious adverse events. The first patient was a Child-Pugh A5 cirrhotic man, started on OCA at the dose of 5 mg/daily. After one month of therapy, he experienced worsening bilirubin and severe pruritus which prompted OCA withdrawal. The liver synthetic function improved, however within a year, he complicated with lung infection and liver failure and deceased. The second patient was a Child-Pugh B7 cirrhotic woman, who started OCA at the dose of 5 mg/week, and presented worsening of bilirubin after nine months, which led to OCA withdrawal. Thereafter, the patient had a partial improvement of liver function, however died for Coronavirus Disease 19 chest infection 8 months after OCA discontinuation. The third patient was a Child-Pugh B9 cirrhotic woman, who initiated OCA at the dose of 5 mg/week, discontinued after four months for worsening bilirubin. After a partial recovery of liver function, she progressively deteriorated and received a liver transplant seven months after OCA withdrawal. Finally, a Child-Pugh A5 cirrhotic woman died within the study period for liver failure after a TIPS placement.

Missed up titrations

We defined missed up-titrations when patients were taking 5 mg/day at 12 months even though they had an ALP ≥ 1.5 UNL at six months and they did not reported pruritus at last follow-up visit.

Considering all the study cohort, among forty-seven patients with ALP value ≥1.5 and absence of pruritus at six months (i.e. eligible for up-titration), 29 (62%) did not up-titrate; 13 (45%) and 2 (7%) of these, achieved response according to Poise criteria and normal range criteria, respectively; out of the 18 patients who did up-titrate, response rate were 5 (28%) and zero, respectively.

Considering cirrhotic patients, out of 14 cirrhotic patients with ALP value ≥1.5 and absence of pruritus at six months (i.e. eligible for up-titration), 12 (86%) did not up-titrate. Among these, 4 and 0 achieved response according to Poise criteria and normal range criteria, respectively; no patient who did up-titrate responded according to both criteria.

Considering PBC-AIH overlap patients, out of 5 patients with ALP value ≥1.5 and absence of pruritus at six months (i.e. eligible for up-titration), 3 did not up titrated, of whom 1 and 0 had a biochemical response according to Poise criteria and normal range criteria, respectively.