**Management of primary biliary cholangitis prior to obeticholic acid availability.**

# Management of primary biliary cholangitis prior to Obeticholic Acid availability. A study from Turin, Italy

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**Running title:** Ursodeoxycolic acid and PBC

**Abstract**

BACKGROUND: Primary Biliary Cholangitis (PBC) is an autoimmune cholestatic liver disease with unknown etiology. The prognosis of patients affected by PBC is heterogeneous, with a relevant improvement achieved after the introduction of ursodeoxycolic acid (UDCA). Since in the last years obeticholic acid (OCA) has been approved for the combined treatment of PBC, in patient non-responders to UDCA or as monotherapy in those intolerant to UDCA, we evaluated the response to UDCA in a cohort of patients with PBC managed in a specialistic setting.

METHODS: We included 38 UCDA-treated non-cirrhotic, early-PBC patients. Data were retrieved from documents compiled during the annual follow-up. The response to therapy was assessed comparing the parameters of our cohort with the inclusion criteria of the POISE trial and the Paris I and Paris II criteria.

RESULTS: The cohort included 34/38 female patients and the average age was 65.34±10.69 years. Over 50% of the patients were affected by at least one disease associated to PBC. Using the POISE criteria and the Paris I and Paris II criteria, we identified 5, 2 and 5 non-responders**,** respectively. All patients with severe fibrosis had a biochemical response to UDCA according to the three different criteria applied. No side effect was reported.

CONCLUSIONS: We confirm that UDCA is a safe and effective treatment in patients with PBC. Non-responder patients represent 13% of our population, with high risk of disease progression and complications. In this context, further therapy using OCA should be considered.

**Key words:** Primary biliary cholangitis – Primary biliary cirrhosis - Ursodeoxycolic acid - Obeticholic acid

## Introduction

The epidemiology of chronic liver diseases has been rapidly changing in the current decade due to the decrease in rate of viral hepatitis and the increase in new epidemic of a wide spectrum of metabolic disorders. This is the consequence of the extensive diagnosis and diffuse treatment of hepatitis C virus and hepatitis B virus.[1-3] On the other hand, the epidemiology of liver diseases arising from other etiologies has not substantially changed.

Primary Biliary Cholangitis (PBC, formerly known as Primary Biliary Cirrhosis) is a chronic inflammatory autoimmune cholestatic liver disease with unknown etiology, entailing a T lymphocyte-dependent destruction of cholangiocytes in the interlobular bile ducts. The immune-mediated bile duct injury and the proliferation of residual cholangiocytes lead to the loss of bile ducts, and bile acids retention, with consequent hepatocyte damage. The liver damage slowly progresses towards fibrosis, at first localized in portal and periportal areas, and then diffuses to the entire parenchyma, subsequently leading to end-stage liver disease.[4,5] Liver transplantation is the ultimate cure for end-stage liver diseases. However, due to shortage of donor livers, lately, much hope has turned towards cell transplantation, Bioartificial Liver (BAL) systems and tissue/organ bioengineering, mainly as a bridging therapy, for alleviating complications associated to end-stage liver diseases.[6]

PBC is a rare disease, with an estimated incidence and prevalence ranging from 0.3-5.8 per 100 000 and 1.9-40.2, respectively, in the European population.[7] The onset of PBC typically occurs between 30 and 65 years old, patients refer to the doctor mainly because of pruritus or asthenia, even if initially the disease is often symptomless.[8] In rare cases, cirrhotic manifestations, such as ascites, bleeding varices and hepatic encephalopathy, are present at the diagnosis.[9] In recent decades, a pattern of PBC presentation consistent with an older age at diagnosis (from 46.9 years in the 1970s to 57.0 years from 2010 onward) alongside reduced disease severity has been reported.[10]

Criteria for establishing the diagnosis of PBC include: biochemical evidence of cholestasis based mainly on serum alkaline phosphatase (ALP) elevation, supported by simultaneous serum gamma glutamyltranspeptidase (GGT) elevation; presence of antimitochondrial antibodies (AMA); histologic evidence of non-suppurative destructive cholangitis and destruction of interlobular bile ducts (Class I, Level B).[11,12] Liver biopsy is not essential for the diagnosis of PBC in patients with high AMA titres, but allows, when necessary, activity and stage of the disease to be assessed (III/A1). The clinical course of PBC is characterized by the development of cholestasis-related complications, as malabsorption, D vitamin deficiency, osteoporosis, dyslipidemia, and by the slow evolution towards cirrhosis. Nevertheless, a significant proportion of patients shows normal laboratory parameters, without symptoms or complications. These cases are defined "early PBC" and are characterized by a very slow disease evolution.[13]

The prognosis of patients affected by PBC is heterogeneous, with a relevant improvement achieved through the introduction of Ursodeoxycolic Acid (UDCA). Several studies demonstrated that UDCA is a safe and effective therapy and improves both biochemical parameters and long term survival. Moreover, the use of UDCA has been associated with a reduction in serum LDL-cholesterol levels, a lower risk of developing varices, and slower histologic progression. Therefore, UDCA at dose of 13-15 mg/kg/day orally is recommended for patients with PBC who have abnormal liver enzyme values regardless of histologic stage (Class I, Level A).[11] In fact, treatment of early-stage disease patients with UDCA increases their survival to a rate comparable to that of the general population.[14]

In 2016, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved Obeticholic Acid (OCA) for the combined treatment of PBC in patient non-responders to UDCA or as monotherapy in those intolerant to UDCA. This drug enhances the activation of farnesoid X receptors, whose signaling reduces bile acid synthesis and stimulates choleresis, protecting hepatocytes from bile acid toxicity.[15] In view of these new therapeutic

perspectives, we evaluated the response to UDCA and the possible indications for treatment with OCA in a cohort of patients with PBC managed in a specialistic setting.

## Materials and Methods

### *Population*

Patients with PBC followed at the Hepatology Day Service of the Internal Medicine Unit III of Molinette Hospital (Città della Salute e della Scienza), Turin (Italy), from January 2016 to December 2017, were included in this study. Patients with end-stage liver diseases arising from PBC were referred to the Unit of Gastroenterology (dedicated to this issue) of the same Hospital and were not included in this data collection. This choice is due to the poor prognosis of these patients, with the need to address part of them for liver transplantation.[16] We also excluded PBC cases associated with viral infections, hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency, autoimmune hepatitis (AIH), nonalcoholic steatohepatitis (NASH), metabolic disorders and toxic abuse (in particular alcohol abuse).[1,17]

### *Data collection*

All patients were subjected to annual follow-up, including clinical assessment and laboratory tests. Data were retrieved from documents compiled during the annual follow-up. The following clinical and biochemical information were collected: date of birth, sex, date of PBC diagnosis, liver biopsy (if requested), UCDA dosage and treatment duration, baseline AMA levels, baseline and yearly biochemistry (serum alanine aminotransferase or ALT, aspartate aminotransferase or AST, albumin, ALP, total bilirubin, GGT, lipids, vitamin D and thyroid stimulating hormone or TSH). Data on echography and transient elastography (TE) were also gathered.

The response to UCDA therapy was assessed comparing the parameters of our cohort with the inclusion criteria of the POISE trial[18] and with Paris I[19] and Paris II[20] criteria.

## Results

### *Characteristics of study population*

The study cohort included 38 UCDA-treated non-cirrhotic, early-PBC patients, without significant complications, with only two reporting pruritus and one asthenia. Of this cohort, 89.5% were female (N: 34) with a female:male ratio of 8.5:1 and the average age was 65.34±10.69 years. A large proportion of these patients (over 50%) was affected by at least one disease associated to PBC: 16 were affected by one co-morbidity, 4 by two co-morbidities, 2 by three co-morbidities and 2 by four co-morbidities. These included autoimmune thyroiditis, which was the most frequent co-morbidity, Sjögren Syndrome, Raynaud's phenomenon, AIH, diabetes insipidus, osteopenia and osteoporosis. Eight patients were affected by osteopenia or osteoporosis: four of them were more than 65 years old while 3 were between 50-65 years, and one was younger than 50. In addition, 11 patients, despite no bone disease, showed D vitamin deficiency and were treated with cholecalciferol. Other deficiencies found in this population were those of B12 vitamin (one patient) and folic acid (two patients).

### *Biochemical data*

Thirty-three patients were AMA positive. According to the European Association for the Study of the Liver (EASL) guidelines,[8] a diagnosis of PBC can be made in adult patients with otherwise unexplained elevation of ALP and presence of AMA (≥1:40) and/or AMA type M2. For the 5 AMA-negative patients, a bioptic sample was requested to ascertain the diagnosis of PBC. Among these, three patients were affected by AIH-PBC overlap syndrome.

Table I shows biochemical liver tests of patients, with their mean values and standard deviation (SD). We highlight the large variability of AST, ALT, GGT and ALP levels, which had high SD. As expected, total bilirubin, albumin and international normalized ratio (INR) of prothrombin time mean values were within the range of normality, pointing out to normal liver function. Seventeen of the 38 patients did not show outlier in liver function tests. In the other cases, abnormalities mainly involved

GGT and ALP levels with or without increase in AST, ALT and total bilirubin levels. Moreover, 18 patients showed increased levels of total cholesterol (>200 mg/dl), with 8 of them having high levels of HDL-cholesterol (>60 mg/dl), 2 having normal HDL (40-60 mg/dl) and 2 showing a reduction in HDL (<40 mg/dl) levels.

***UCDA response***

All patients were treated with UDCA at a dose of 13-15 mg/kg/day. For those with overlap syndromes, the immunomodulatory agents, prednisone and azathioprine, were associated. TE showed absent or mild fibrosis (F0/F1) in most patients, with three patients showing significant fibrosis (F2), four showing severe fibrosis (F3) and none cirrhosis (F4). Among patients with severe fibrosis, biochemical tests revealed two cases with normal values, one case with a modest increase in GGT (65 U/L; normal value: 10-50 U/L), while the fourth was characterized by ALP levels higher than the upper limit of normality (184 U/L, n.v.: 63-128 U/L).

The response to therapy was assessed by comparing the parameters of our cohort with those used in the POISE trial[18], which is the phase III trial of OCA, and with the Paris I[19] and Paris II[20] criteria. Table II shows the three models (POISE, Paris I and Paris II) used to evaluate the response to UDCA therapy. Using the POISE criteria, we identified 5 non-responders**,** while the Paris I and Paris II criteria identified, respectively, 2 and 5 non-responders. The POISE trial criteria identified all non-responders defined by the other two criteria, except one patient (Patient 17), which was identified as a non-responder only by Paris II criteria. Paris I criteria, on the other hand, identified only 2 non-responders found by POISE criteria (Patients 4 and 30). Paris II criteria identified most POISE-derived non-responders, except for one patient (Patient 30). Interestingly, all patients with severe fibrosis had a biochemical response to UDCA according to the three different criteria applied (Table III). No side effect was reported.

## Discussion

The biochemical response to the first-line therapy with UDCA can be assessed through different criteria, including Barcelona criteria,[21] Paris I[19] and Paris II[20] criteria, Rotterdam criteria[22] and Toronto criteria.[23] These criteria are useful at the beginning of UDCA therapy in identifying patients who will fail to develop an appropriate biochemical response to UDCA. It has been observed that up to 40% of patients does not develop an appropriate response to the standard therapy, with an increased risk of disease progression and cirrhosis development. There is currently no consensus on the treatment of these non-responder patients. Thus, the definition of safe and effective second-line therapies for non-responders to UDCA is urgently needed.

Several therapies have been evaluated over the years for PBC treatment, including the association of UDCA with budesonide,[24,25] colchicine,[26] azathioprine,[27] rituximab,[28,29] chlorambucil[30] and drugs contrasting bile acids accumulation, such as bezafibrate.[31,32] Several trials and meta-analyses have studied the role of fibrates in PBC treatment, and in 2017, the first large randomized trial (the "Bezurso" study) was published, evaluating the effectiveness of UDCA-bezafibrate combination in patients with a suboptimal response to UDCA. This trial showed an important benefit of UDCA-bezafibrate therapy in terms of biochemical response, and the incidence of adverse events was not statistically higher compared to that of the UDCA-placebo group.[32]

Efficacy and side effects of the recently approved OCA were studied in several phase II trials and in the phase III trial POISE, which included patients with a suboptimal response to UDCA and those who did not tolerate UDCA. Patients received OCA at a dose of 10 mg (the 10-mg group), OCA at a dose of 5 mg with adjustment to 10 mg if applicable (the 5-10 mg group), or placebo. After 12 months, 46% of the 5-10 mg group, 47% of the 10 mg group and 10% of the placebo group reached the primary endpoint. The most frequent side effect was pruritus, with a lower incidence in the 5-10 mg group.[18] OCA, proved to be safe and effective, is now recommended in association with UDCA in patients with inadequate response to the standard therapy or in monotherapy in patients who did not tolerate UDCA.

The population included in our study was composed of non-complicated PBC patients, most often asymptomatic. Despite the apparent small sample size, considering that PBC is a rare disease, the strength of this study was the homogeneous features of the included cohort. All patients were treated with UDCA without side effects. In our study, 13% evaluated by POISE criteria did not respond to 13-15 mg/kg/day UDCA and this percentage changed to 5% and 13%, respectively, when the Paris I or Paris II criteria were applied. Since the POISE trial criteria have been used to select patients for the phase III trial with OCA, they allowed us to identify 5 non-responders, for whom OCA may be recommended. When compared to Paris I and Paris II criteria, the POISE trial criteria identified all non-responders defined by the 2 classification systems, except for one patient, who was identified as non-responder only by Paris II criteria, and whose ALP level was higher than the Paris II cut-off and lower than POISE trial cut-off. This comparison raises some concerns, in terms of definition of the response to therapy. For example, Paris I cut-off for ALP and AST levels is higher than those of other criteria, and both patients identified by Paris I criteria were defined as non-responders only because of the bilirubin level, which was higher than the upper limit of normality.[19] Regarding Paris II criteria instead, these are used in early PBC and are appropriate for this population, which is composed of non-complicated and mainly asymptomatic PBC patients.[20]

In agreement with previous studies, our findings confirm the importance of TE in PBC management, as shown for other liver diseases.[33] The majority of our population showed absence of or mild fibrosis and no one had cirrhosis. However, three patients showed significant fibrosis and four severe fibrosis. Considering that biochemical liver tests in patients with severe fibrosis were normal or characterized by mild changes, the importance of performing TE in patients with normal liver tests as well as in clinically advanced PBC is evident. Non-responders showed a mild/significant fibrosis.

Among the 38 patients under study, 8 were affected by osteopenia or osteoporosis, and 10 showed vitamin D deficiency and were treated with cholecalciferol. It has been shown that the development of metabolic bone disease in PBC patients is caused not only by vitamin D deficiency,

but also by the inhibition of osteoblasts differentiation and function due to increased unconjugated bilirubin.[34] On the other hand, the pathogenesis of osteopenia and osteoporosis is multifactorial,[35] and both age and female sex are important risk factors for these diseases. To this regard, it is crucial to consider that our population was mainly composed of females and the average age was 65.34 years. According to both European[8] and American[12] guidelines, bone mineral density should be assessed by bone densitometry in chronic cholestatic liver disease. EASL guidelines, in particular, recommend dual-energy X-ray absorptiometry (DEXA) at presentation and during the follow-up, with a frequency depending on degree of cholestasis or other individual risk factors.[8]

The clinical profile of the population was influenced by the presence of autoimmune co-morbidities. The most frequent was autoimmune thyroiditis, followed by Sjögren syndrome, Raynaud's phenomenon, AIH and nephrogenic diabetes insipidus, which can be considered as an extraglandular manifestation of the Sicca syndrome. This form of Sjögren syndrome has been previously reported[36-38] and two patients in the present study were affected by diabetes insipidus in association with Sjögren syndrome. Three patients were affected by PBC-AIH overlap syndrome and their therapy included both UDCA and immunomodulatory agents. In these forms, the clinical presentation is variable, with an overlap of clinical and biochemical features of the two diseases. The diagnosis requires the use of criteria establishing the presence of both diseases, defined by liver enzymes levels, cholestasis markers, serological tests (AMA, antibody anti-smooth muscle, IgG2) and, where appropriate, liver biopsy.[39] The recommended therapeutic approach is represented by combined therapy with UDCA and corticosteroids (III/C2), an alternative option is an initial treatment with UDCA and the association of corticosteroids in case of inadequate response during the first three months (III/C2). In case of necessity of long-term immunosuppression, steroid sparing agents should be considered (III/C2).[8] Regarding the prognosis of PBC-AIH overlap syndrome, currently there are no large trials defining the clinical course of these patients, but some observational data showed that the response to UDCA was similar to PBC patients.[11,40] Among the three patients with overlap syndrome in our population, two had a complete response to UDCA,

while one did not. Moreover, some studies reported a higher risk of cirrhosis-related complications in patients affected by overlap syndrome compared to those with exclusive PBC.[41] Therefore, a close monitoring and an adequate therapy are necessary in order to prevent or slow down the development of cirrhosis, and complications of cirrhosis should be promptly identified and treated.

In conclusion, the majority of patients with early PBC develops an adequate biochemical response to UDCA, without side effects. Thus, in accordance with previous studies, we confirm that UDCA is a safe and effective treatment in most patients. In addition, we emphasize the necessity of second-line therapeutic strategies for non-responder patients. These represent 13% of our population, with high risk of disease progression and complications. In this context, further therapy using OCA should be considered.

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| **Patients** | **N=38** |
|---|---|
| Age, years | 65.34 (10.69) |
| Female, n (%) | 34 (89,5%) |
| AMA+, n (%) | 33 (87%) |
| Degree of Fibrosis, n(%) | |
| F 0/1 | 31 (81.6%) |
| F 2 | 3 (7.9%) |
| F 3 | 4 (10.5%) |
| F 4 | 0 (0%) |
| AST, U/l | 29,53 (23,30) |
| ALT, U/l | 33,32 (43,43) |
| GGT, U/l | 67,61 (83,77) |
| ALP, U7l | 105,31 (64,75) |
| Bilirubin, mg/dl | 0,69 (0,31) |
| Albumin, g/dl | 4,35 (0,41) |
| INR | 0,98 (0,06) |

Table I. - Features of the study cohort

Legend: AMA, anti-mitochondrial antibodies; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; ALP, alkaline phosphatase; INR, international normalized ratio of prothrombin time

| | | |
|---|---|---|
| POISE Trial | - ALP≥ 1.67ULN<br>- ULN< Bilirubin < 2ULN | - ALP≥ 213.76 U/l<br>- Bilirubin:1.0-2.0mg/dl. |
| Paris I criteria | - ALP≥3ULN<br>- AST≥2 ULN<br>- Bilirubin >ULN | - ALP ≥384 U/l<br>- AST ≥ 90 U/l<br>- Bilirubin> 1 mg/dl |
| Paris II criteria | - ALP≥1,5 ULN<br>- AST ≥1,5 ULN<br>- Bilirubin>ULN | - ALP≥192 U/l<br>- AST≥ 67.5 U/l<br>- Bilirubin> 1 mg/dl |

Table II. - Criteria considered in the POISE Trial and Paris I and Paris II criteria

| | Degree of Fibrosis | POISE trial | Paris I | Paris II |
|---|---|---|---|---|
| Patient 1 | F2 | Responder | Responder | Responder |
| Patient 2 | F 0/1 | Responder | Responder | Responder |
| Patient 3 | F3 | Responder | Responder | Responder |
| Patient 4 | F 0/1 | Non responder | Non responder | Non responder |
| Patient 5 | F 0/1 | Responder | Responder | Responder |
| Patient 6 | F 0/1 | Responder | Responder | Responder |
| Patient 7 | F 0/1 | Responder | Responder | Responder |
| Patient 8 | F 0/1 | Responder | Responder | Responder |
| Patient 9 | F 0/1 | Responder | Responder | Responder |
| Patient 10 | F 0/1 | Responder | Responder | Responder |
| Patient 11 | F 0/1 | Responder | Responder | Responder |
| Patient 12 | F 0/1 | Responder | Responder | Responder |
| Patient 13 | F 0/1 | Responder | Responder | Responder |
| Patient 14 | F 3 | Responder | Responder | Responder |
| Patient 15 | F 0/1 | Responder | Responder | Responder |
| Patient 16 | F 0/1 | Responder | Responder | Responder |
| Patient 17 | F 0/1 | Responder | Responder | Non responder |
| Patient 18 | F 0/1 | Responder | Responder | Responder |
| Patient 19 | F 0/1 | Responder | Responder | Responder |
| Patient 20 | F 0/1 | Non responder | Responder | Non responder |
| Patient 21 | F 0/1 | Responder | Responder | Responder |
| Patient 22 | F 2 | Non responder | Responder | Non responder |
| Patient 23 | F 0/1 | Responder | Responder | Responder |
| Patient 24 | F 0/1 | Responder | Responder | Responder |
| Patient 25 | F 3 | Responder | Responder | Responder |
| Patient 26 | F 3 | Responder | Responder | Responder |
| Patient 27 | F 0/1 | Responder | Responder | Responder |
| Patient 28 | F 0/1 | Responder | Responder | Responder |
| Patient 29 | F 0/1 | Responder | Responder | Responder |
| Patient 30 | F 2 | Non responder | Non responder | Responder |
| Patient 31 | F 0/1 | Responder | Responder | Responder |
| Patient 32 | F 0/1 | Responder | Responder | Responder |
| Patient 33 | F 0/1 | Responder | Responder | Responder |
| Patient 34 | F 0/1 | Responder | Responder | Responder |
| Patient 35 | F 0/1 | Responder | Responder | Responder |
| Patient 36 | F 0/1 | Responder | Responder | Responder |
| Patient 37 | F 0/1 | Non responder | Responder | Non responder |
| Patient 38 | F 0/1 | Responder | Responder | Responder |

Table III. - Results of the study based on the considered criteria (POISE trial, Paris I and Paris II).