# UNIVERSITÁ DEGLI STUDI DI PADOVA

# CORSO DI LAUREA MAGISTRALE IN MEDICINA E CHIRURGIA

DIPARTIMENTO DI SCIENZE CHIRURGICHE, ONCOLOGICHE E GASTROENTEROLOGICHE

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**TESI DI LAUREA**

## QUALITY OF LIFE AND CLINICAL OUTCOMES IN PEOPLE WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH OBETICHOLIC ACID: RESULTS OF A PHASE 4, REAL-LIFE OBSERVATIONAL TRIAL

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ANNO ACCADEMICO 2022-2023

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# List of abbreviations

AE2: anion exchanger 2

AIFA: Agenzia Italiana del Farmaco

AIH: autoimmune hepatitis

ALP: alkaline phosphatase

ALT: alanine aminotransferase

AMA: anti-mitochondrial antibodies

ANA: anti-nuclear antibodies

AST: aspartate aminotransferase

CD: cluster of differentiation

CNS: central nervous system

EQ-5D-5L: EuroQoL 5D-5L

FIS: Fatigue Impact Scale

FXR: Farnesoid X receptor

GGT: gamma-glutamyl transpeptidase

GWAS: Genome-wide association studies

HCC: Hepatocellular carcinoma

HRQoL: health-related quality of life

IFN: interferon

Ig: immunoglobuline

IL: interleukin

INR: International Normalized ratio

LSM: liver stiffness measurements

MRCP: magnetic resonance cholangiopancreatography

NASH: non-alcoholic steato-hepatitis

NK: natural killer

OCA: obeticholic acid

PBC: Primary Biliary Cholangitis

UDCA: Ursodeoxycholic acid

ULN: upper limit of normal

VAS: Visual Analogue Scale

VCTE: Vibration-controlled transient elastography

# Abstract

**Introduction:** Primary biliary cholangitis (PBC) is a chronic cholestatic autoimmune liver disease, which, if left untreated, can lead to cirrhosis. It can be associated with impaired health-related quality of life (HRQoL) caused by symptoms, mainly pruritus and fatigue, and eventually depression. Treatment confidence is a significant and modifiable variable in HRQoL of PBC people, and UDCA has been reported to be a positive factor in enhancing trust therapy. No real-life data on this and HRQoL exist regarding obeticholic acid (OCA), a second-line therapy, which can also lead to new-onset or worsening of pruritus.

**Aim:** To assess the impact of OCA on biochemistry, patients' illness perception and HRQoL of PBC patients.

**Methods:** We designed a phase 4 observational open label study (Protocol AOP1515) and collected at baseline and every 6 months from starting OCA, biochemistry, adverse events, reported symptoms and the results of following questionnaires: PBC-40, Fatigue Impact Scale (FIS), 5-D Itch scale, EuroQoL-5D-5L. Changes in symptoms after OCA introduction were assessed by Wilcoxon paired rank test.

**Results:** Nineteen (4 with cirrhosis) over 32 patients who started OCA treatment between March 2018 and April 2022 for insufficient response to UDCA agreed to participate. The median duration of OCA treatment was 32 (24-58) months with no drug discontinuation due to adverse events. A decrease of alkaline phosphatase below 1.5 x ULN and 1 x ULN was observed in 47%, 67%, 64%, 67% and 16%, 21%, 35%, 17% patients at 6, 12, 18, 24 months, respectively. Significant reductions of gGT, AST and ALT were observed at every time point from 6 to 48 months. Total bilirubin decreased at every timepoint reaching statistical significance from 6 to 24 months of treatment. Non significant reduction in liver stiffness was observed at 12, 24, 36 and 48 months. After 6,12,18 and 24 months of treatment 38.5%, 33.3%, 33.3% and 50.0% of patients matched POISE primary end point criteria, while 28.6%, 33.3%, 33.3% and 38.5%, at the same timepoints, matched PARIS-II criteria.

At the time of starting OCA, clinically significant (moderate and severe) pruritus, fatigue, cognitive and social dysfunction, emotional impairment, and general

symptoms were present in 5%, 32%, 11%, 53%, 37%, 21% patients, respectively. During periodical clinical assessments, all patients reported a significant and persistent general improvement after OCA introduction.

No severe aggravation of itch nor other symptoms was observed after OCA introduction. A trend over a significant reduction of fatigue evaluated by FIS at 36 months was also observed (45[0-82] *vs.*10.5[0-42], p=0.06). Three patients experienced new onset of pruritus of mild severity after OCA introduction that required starting specific therapy (1 fibrate, 1 sertraline and 1 cholestyramine), but in none OCA discontinuation, nor reduction was needed.

**Conclusion:** People with PBC and insufficient response to UDCA experienced a biochemical and subjective improvement after OCA introduction and no significant aggravation of objectively assessed symptoms and measures of HRQoL.

# Introduction

Primary Biliary Cholangitis (PBC) is a chronic cholestatic autoimmune liver disease characterized by serologic positivity to AMA or specific ANA antibodies and histological evidence of chronic non-suppurative, granulomatous, lymphocytic small bile duct cholangitis (1).

If left untreated, PBC progresses to cirrhosis and end-stage liver disease and for this reason, until 2015, it was known as primary biliary cirrhosis (2).

# Epidemiology

Incidence rates of PBC range from 0.84 to 2.75 per 100.000 inhabitants per year, globally. In Europe, incidence is 1.86 per 100.000 per year with different patterns in each sub-continental area: Eastern Europe (0.77), Western Europe (2.26), Northern Europe (1.83) and the South (2.09) (3).

PBC affects almost exclusively adults, with paediatric presentation being anecdotal; one of the youngest reported patients is a 15-year-old girl. South-Korean data show an age-adjusted incidence that increases from 0.45 per 100.000 in 20-29 years old patients to 20.10 in patients aged 70 (4).

According to data collected by the Global PBC study group, 72% of people present with early-stage disease at the time of diagnosis (5). Global prevalence of PBC is estimated to be 14.6 (1.91-40.2) per 100.000 population, increasing in the last year due to incidence and survival outpacing death. In the European population the prevalence is slightly lower and varies from 3.2-20.7 per 100 000 (4).

# Risk factors for PBC

## Female gender

Primary biliary cholangitis affects more frequently women than men: in Danish and Italian cohorts, incidence in women is 2.3 times higher than that observed in men but women present higher rates of survival after 10 years of observation (67% vs 47%, in Lombardia) (6,7).

## Familial risk

Autoimmune liver disease presents a gene-gene/gene-environment interactions

rather than classical Mendelian inheritance. Risk-associated genes have been identified, most being pleiotropic across the other autoimmune diseases and influence the risk of developing the disease also according to environmental exposures. Prevalence among first-degree relatives of PBC patients is 100-fold greater than that in unrelated comparator populations (8). Concordance among monozygotic twins reaches 60%; and 6% of patients have a relative affected by the same disease(9).

### Clinical heterogeneity is evident epidemiologically.

AMA positive patients, with normal levels of Alkaline phosphatase are likely to develop PBC. Multicentric cohort studies have shown that 75% of these people develop disease in a time span of 18 years(10,11).

A recent large study conducted by the French Immunology Network, reported an AMA seroprevalence in patients without evidence of PBC of 16.1 per 100.000 people and less than half of them developed PBC over time (with no prior diagnosis of PBC) and with a reported 5-year incidence rate of PBC of 16% (12).

The age at the time of PBC diagnosis appears to be a leading factor in response to first-line therapy with UDCA in fact younger people (aged under 45) show a poor biochemical response (< 50%)

# Etiopathogenesis

Even if the autoimmune origin of the disease is undoubtable, immunosuppressive therapy is ineffective since bile composition has a central role in the pathogenesis.

### Autoimmunity

PBC is a chronic and progressive liver disease characterized by autoimmune response directed against biliary epithelial cells. Causing factors are unknown, but it is clear that both genetics and environment interplay a key role in the development of the disease (13). Understanding the pathogenesis of the disease is crucial for developing new weapons to treat the disease. Animal models have given such a possibility showing that interferon (IFN) signalling is involved. The immuno-regulatory pathway includes interleukin (IL)-12 and Janus kinase/signal trans-dicer and activator of transcription (JAK-STAT) signalling, as well as the human leukocyte antigen (HLA) locus. Moreover, immune injury enhances cholestasis as

fast as AE2 (Cl-/HCO3- exchanger - anion exchanger 2) and biliary glycocalyx are downregulated by the autoimmune response, causing invasion of hydrophobic bile acid monomers (14,15).

**Autoantibodies**

Anti-mitochondrial autoantibodies (AMA) and disease-specific anti-nuclear antibodies (ANA) can be found in patients affected by PBC. The association of AMA antibodies with PBC is highly specific and was firstly described in 1965 by Walker, Doniach, Roitt and Sherlock. This epochal discovery allowed physicians to recognize the disease at a much earlier stage.

PBC-specific ANA autoantibodies are also observed in PBC in one third of the patients. These PBC-specific ANA autoantibodies are characterized by indirect immunofluorescence on Hep-2 cells by multiple nuclear dots (MND) or rim-like/membranous (RLM) patterns and are directed against two proteins of the nuclear envelope, gp210 and p62 (MND pattern), or against nuclear antigens, sp100 (RLM).

The prognostic value of PBC-specific ANA autoantibodies is controversial, however they seems to correlate with a more severe phenotype of PBC (16,17).

**Innate immunity**

Genome-wide association studies (GWAS) have allowed researchers to identify single nucleotide polymorphisms (SNPs) which are responsible for the involvement of innate immunity in PBC. Those SNPs are located in genes encoding proteins critical for the proper functioning of mononuclear phagocytes (dendritic cells, macrophages, monocytes) and IFN regulatory factors 5 and 8 and interleukin-12A (IL-12A).

There are two parallel macrophage systems both involving CD68. Interestingly, CD68+ cells have been detected in and around injured bile ducts in PBC. Moreover, comparing PBC patients to controls, it has been described that peripheral blood monocytes produce a higher amount of pro-inflammatory cytokines. None of the two phenomena regarding monocytes has a clear explanation.

Liver resident natural killer cells represent about 30% of hepatic lymphocytes, being the major players of the hepatic innate immune system. Compared to circulating NK, liver-resident ones present a different pattern of expression of

homing receptors such as CCR5 and CXCR6 (15,18,19).

**Adaptive immunity**

TLR-3 mediated NK stimulation and TLR-4-mediated monocyte stimulation are the initiative factors of NK cell cytotoxicity against BECs. NK cells do not directly attack BECs, but surrounding them, and secrete IFN-gamma, inducing the expression of HLA-1 by BECs and the exposure of PDC-E2, which is recognized by T-cells as auto-antigen, perpetuating bile duct injury. In these terms, NK cells establish a bridge between innate and adaptive immunity (19,20).

**Alloimmunity and autoimmunity**

Bile ducts are affected both by autoimmune (*i.e*. PBC and PSC) and allogenic (*i.e.* graft versus host disease) diseases, moreover, there is a clear evidence of recurrence of PBC after liver transplantation (LT) (21). The common histological background of these two phenomena is the vanishing bile duct phenotype, but probably this has a different pathogenesis and in PBC is mediated by epithelial cytolysis and senescence.

Different cytokines drive different phases of inflammation in PBC, perpetuating and progressively worsening inflammation. Firstly, traumatized epithelium produces IL-33 and IL-25 driving T-cells response towards Tregs and Th2; secondly Th1 and Th17 T cell responses are activated by IL-1b, IL-6, TNF-a, CCL20 and type 1 interferons. All these molecules represent potential targets for therapy and explain the common underground for allo- and autoimmune responses (19,22).

## Cholestasis

Despite the clear evidence that PBC is an autoimmune disease, it does not respond to immunosuppressive therapy, otherwise it has a good response to a choleretic bile acid (UDCA). This observation highlights the key role played by the bile composition in the etiopathogenesis of PBC. More specifically, biliary bicarbonate secretion, regulated by bicarbonate-chloride exchanger protein (also known as anion exchanger 2 - AE2) localized on the apical membrane of large cholangiocytes, buffers the millimolar and extremely high concentrations of hydrophobic bile acids along with the micelles made up by cholesterol and phospholipids. A reduction of AE2 expression and activity has been documented in

patients affected by PBC. The regulation of the expression of AE2 appears to be controlled by microRNA 506 (miR-506), encoded by chromosome X (23). In PBC patients, miR-506 is upregulated, consequently AE2 is down-regulated, along with type III inositol 1,4,5-trisphosphate receptor, a central player in the regulation of cholangiocyte secretory capacity (24).

Moreover, the decrease of bicarbonate secretion leads to an increase of biliary concentration of protonated bile acids, invading cholangiocytes and leading them to apoptosis (25).

Treatment with UDCA restores the secretin response and furthermore the association of UDCA and steroids upregulates AE2 expression (14).

### Ductopenia

Chronic portal inflammation in PBC causes ductopenia, which does not happen in portal inflammation due to other aetiologies (e.g., HCV). Progressive ductular inflammation subverts the normal anatomy of the basement membrane of the biliary epithelia and promotes obliteration of the vessels of the peribiliary plexus, these two factors lead to ischemia, which contributes to biliary duct damage. Inexplicably, in some cases or late on disease stage repair and recovery of the epithelium do not occur, leading to ductopenia (19,26).

### Ductular reaction

Ductular reaction represents a driving factor of cholestatic disease progression. Several cells are involved in the process, such as hepatic progenitor cells, reactive ductular cells and intermediate hepatobiliary cells. Those cells do not have regenerating potential anymore, this leads to fibrosis, senescence, and in PSC even to carcinogenesis (27).

## Microbiome

Different studies have been conducted recently regarding the connection between microbiome and PBC. However, those studies are limited by different confounding factors, first of all diet and lack of knowledge about normal microbiome. A Chinese cross-sectional GWAS in PBC patients has recently identified new risk loci and has documented a reduction in species richness and alteration in 12 genera (28).

# Histology

PBC is characterized by chronic, non-suppurative destructive cholangitis (CNSDC), which is responsible for the destruction of interlobular and septal bile ducts, leading to the so-called “florid duct lesions". T-cells associated with few B-cells, macrophages and eosinophils make up the inflammatory infiltrate. In a limited number of cases, epithelioid granulomas may be present. Progressive damage of the bile ducts ends up in ductopenia, inflammation and collagen deposition; all those characteristics are used in order to establish the histological severity of the disease.

## Staging systems

Characterizing the entity of the damage that the biliary tract undergoes is crucial both in therapeutic and prognostic terms. It has been widely demonstrated, in fact, that UDCA therapy has a significant impact on the grade of alterations detected (29).

Different staging systems have been proposed for PBC throughout the years: the most dated one was proposed by Rubin et al., followed by Scheuer and Lefkowitch, Popper and Schaffner, Ludwig (1978) staging systems (30). More recently, a new system has been developed by Y. Nakanuma et al. (31) which takes into account not only histologic components but also the assessment of chronic cholangitis and hepatitis activity.

### Staging

From the very beginning, three fundamental histological marks have been considered and were included in Nakanuma staging system, that being:

1. Fibrosis, which reflects the progression of chronic liver disease and being the driving factor of cirrhosis and ultimately of the uprising of Hepatocellular carcinoma (HCC).
2. Bile duct loss: a characteristic element found in PBC, due to progressive immune-related bile damage.
3. Deposition of orcein-positive granules, which represent a marker of chronic cholestasis ascribable to the presence of copper-binding lysosomes and their deposition (32).

Each item is graduated from zero to 3 points resulting in a total score which can be evaluated as follows:

- Total score 0: stage 1, no or minimal progression.
- Total score 1 - 3: stage 2, mild progression.
- Total score 4 - 6: stage 3, moderate progression.
- Total score 7 - 9: stage 4, advanced progression (i.e., cirrhosis).

**Grading**

As previously mentioned, in 2010 Nakanuma et al. proposed a new staging and grading system which included two crucial characteristics of necroinflammatory lesions of PBC (33):

1. Chronic cholangitis activity, including CNSDC (CA 0-3): described as different grades of ductal epithelial damage due to cholestasis that involves no (CA 0), <⅓ (CA 1), ⅓ - ⅔ (CA 2) or >⅔ (CA 3) of the portal tracts included in liver biopsy.
2. Hepatitis activity: evaluated as the presence of interface and lobular hepatitis; their activity was graduated from HA 0 (no activity) to HA 3 (marked activity, described as Interface hepatitis affecting 20 continuous hepatocytes in more than half of the portal tracts, and moderate lobular hepatitis, or bridging or zonal necrosis).

The evaluation tests performed to validate this new grading system demonstrate that there is a strong correlation between laboratory data (*i.e.*, ALP, gGT, AST, ALT) and CA and HA grades. On the other hand, and surprisingly, ANA and AMA titles did not show a connection with grading and staging scores. Moreover, Nakanuma-assessed grading was able to predict the development of cirrhosis-related conditions, with rates increasing according to the stage, with significant differences observed between stage 2 and 3.

Even so, it has to be said that the Scheuer system has shown a better performance in predicting prognosis of PBC patients who are not responders to UDCA therapy (34).

# Clinical manifestations

People with PBC are increasingly diagnosed after the incidental finding of elevated ALP and/or AMA positivity at screening exams or during follow-up for other

autoimmune diseases; for this reason, more than 60% of patients are asymptomatic. Symptomatic patients often complain fatigue (21-85%), pruritus (19-55%), right upper quadrant abdominal pain (8%), anorexia and jaundice (3-10%) (1).

## Fatigue

Fatigue can be defined as an overwhelming sense of tiredness, lack of energy, and a feeling of exhaustion (35). Even though not specific, it is considered to be the most common and disabling symptom for PBC patients and its intensity appears to have a correlation with the severity of the disease (2,36), especially in the end-stage disease.

Fatigue is composed of central and peripheral components. The first one is characterized by lack of self-motivation and intention; the second one, on the other hand, is due to neuromuscular dysfunction and muscle weakness.

### Peripheral fatigue

Peripheral fatigue appears to have a strong bond with the presence of anti-mitochondrial antibodies (AMA), typical of PBC, causing a shift from aerobic to anaerobic metabolism, leading to excessive lactate production. Although, the way how this happens is still unclear; as a matter of fact the depletion of B-cells producing AMA with Rituximab does not improve fatigue in those patients (37,38).

### Central fatigue

Sleep rhythm alterations and memory impairment are frequent in PBC people, even though they do not correlate with the severity of the disease. The pathogenesis of these symptoms is not clear, albeit different studies have documented alterations in the deep grey matter rsFC (39), as a possible result of immune-mediated signalling from the liver to the brain in PBC patients.

Sleep disturbances are extremely common in the general population (10%), presenting as insomnia and excessive daytime sleepiness, affecting prognosis of both healthy and diseased people. Montagnese *et al.* assessed that PBC people show a relatively well-preserved night sleep quality and daytime vigilance, but delayed sleep-wake habits (40). This is probably due to the fact that circadian and homeostatic sleep regulation are misaligned. Interestingly, according to the same group, PBC people who experience trouble falling asleep are also those affected by more severe pruritus.

Despite this evidence, none of the therapies commonly used in people with altered sleep-wake cycles, such as Modafinil, Ondansetron or antioxidant therapy, have proven to be effective.

In addition to that, different studies have proven that liver transplantation improves but does not resolve fatigue issues in PBC people, underlying both that cognitive symptoms have their origin in the CNS and making unjustified the allocation of the organ for such an indication (41,42).

**Prognostic Significance**

Moreover, Björnsson et al. (43) and Jones et al. (44) have suggested that higher fatigue levels, assessed with FIS Scale, at diagnosis are a reliable predictor of unfavourable outcome (*i.e.*, death or liver transplantation at 5-year follow-up); nevertheless, they did not observe a relationship between FIS Scale results and parameters assessing the severity of liver disease.

## Pruritus

Pruritus is the second most common symptom in PBC people, appearing to be a burdensome affection that can dramatically impairs the quality of life of people with PBC. Its pathogenesis is still poorly understood, and several molecules have been summoned up to explain the genesis of this disorder, including bile acids, endogenous opioids, histamine, serotonin and steroid metabolites (45). It has been supposed that mentioned molecules bind their receptors on unmyelinated C-fibres, responsible for itch perception.

Bile acids, which are elevated in cholestatic diseases, bind and activate several receptors such as TGR5, S1P, FXR, PXR, CAR and VDR. Among these, TGR5 and FXR have been strongly implicated in cholestasis-related pruritus, thanks to MRGPRX4 which is expressed on sensory neurons (46). It has to be highlighted, although, that in PBC there is not a strict correlation between circulating total bile acids levels, skin bile acid levels and itch intensity (47). Moreover, it is important to consider the potential role of FXR as pruritogen, as the use of FXR agonists, such as obeticholic acid is strongly associated with *de novo* onset of itch; evidences in this regard are not univocal as the cross-activation of TRG5 by FXR has been documented, nevertheless, injection of TGR5 ligand in volunteers has not led to itch perception.

Also, bilirubin has been reported to activate MRGPRX4, still, people affected by inherited syndromes of hyperbilirubinemia (*i.e.*, Dubin Johnson), even if with life-threatening levels of total bilirubin, do not complain of itch (48).

Kremer *et al.* in 2010 demonstrated that lysophosphatidic acid is a potential candidate as pruritogen in cholestasis (47), as it is related to increased levels of autotaxin (ATX), even if this does not appear to be always a leading cause of pruritus.

Histamine is a well described pruritogen, as it is associated with intense itch in acute allergic reactions, but it is also present at elevated serum levels in cholestatic diseases. It is stored in high amounts in granules of mast cell, whose release is mediated by different molecules among which bile salts (49). This symptom can appear at any stage of disease, even if absent at diagnosis. Interestingly, it has been reported that pruritus improves as liver disease worsens (50).

Common localizations of itch in PBC are limbs, soles and palms (51,52), even though there are not spared locations, with generalized pruritus being not uncommon.

Itch generally modifies its intensity throughout the day showing a circadian rhythm: its intensity it is reported to be higher in the late afternoon, evening and early night. This phenomenon could be explained by the fluctuation of the concentrations of molecules that exacerbate or mitigate pruritus (52).

In women a variation depending on the menstrual and ovarian cycle has been reported, with higher rates of intensity in the premenstrual phase, during hormone replacement therapy and late pregnancy (45,53).

Peculiar skin lesions, in spite of the high levels of histamine (45), have never been reported to be associated with cholestatic pruritus, even if excoriations and *prurigo nodularis* are not uncommon as sequalae of intense scratching (53).

Several studies have assessed the significative impact of itch on health-related quality of life, affecting cognition, fatigue, emotional health, sleep and social life (54).

## Jaundice

Jaundice usually occurs later in the natural course of the disease, is persistent and associated with worse prognosis. It is the clinical result of direct hyperbilirubinemia, defined as a direct/total bilirubin ratio of more than 15–20%,

or a direct bilirubin level above 1.0 mg/dL. The inadequate bile flow results in the accumulation of bile contents, *i.e.* bilirubin and bile acids, in blood (55).

### Extrahepatic Manifestations

There are many pathologies, mainly autoimmune, associated with PBC such as coeliac disease (5-11%), thyroid diseases (e.g., Hashimoto thyroiditis, Graves' disease, multinodular goiter, thyroid cancer, etc.) 5-25% (56), Sicca syndrome (3.5-68%), Rheumatoid arthritis (3%), PSS and CREST (15-19%), renal tubular acidosis (1). Moreover, presence of anti-centromere antibodies confer a >4-fold risk of developing progressive portal hypertensive disease in PBC specifically (57). The incidence of malignancies is also increased in PBC patients, particularly for hepatocellular carcinoma (19x non-PBC people) (58).

## Health related Quality of Life in PBC patients

As discussed so far, there are several concerns regarding health related quality of life (HrQoL) of people with PBC, as it may be dramatically impaired by symptoms (especially itch and fatigue) and other aspects related to the disease (e.g. social isolation) (59). For this reason a regular assessment of symptoms and HrQoL is crucial, as far as their quantification has been proven to help patients coping with disease (60).
For doing so structured and validated questionnaires may be of help.

### PBC-40

Until 2005 the assessment of HrQoL has been demanded to measurements which were created and validated for other diseases, often non-liver diseases. In 2005, Jacoby *et al*. validated a questionnaire, the PBC-40 questionnaire, composed by 40 questions, organized in six domains, regarding the most relevant issues concerning quality of life of PBC people. The six domains include fatigue (11 questions), emotional (3), social (10), and cognitive function (6), general symptoms (7), and itch (3). In order to create this questionnaire, the authors conducted an in-depth structured interview of 30 PBC patients. After a thematic analysis, a pool of questions was derived, which underwent a two-step reduction process. Questions were then converted into statements with five possible answers, graduated,

according to Likert scale, from 1 (least burden of problem) to 5 (greatest burden of problem). PBC-40 was then validated on a cohort of 400 subjects and evaluated on 40 (59). The final domain is reported below (Table 1).

**Table 1. PBC-40 in its 6 domains and 40 questions.**

| ***Domain*** | ***Question*** |
|---|---|
| *Symptoms* | I was able to eat what I liked |
| | I ate or drank only a small amount, and still felt bloated |
| | I felt unwell when I drank alcohol |
| | I had discomfort in my right side |
| | I had dry eyes |
| | My mouth was very dry |
| | I had aches in the long bones of my arms and legs |
| *Itch* | Itching disturbed my sleep |
| | I scratched so much I made my skin raw |
| | I felt embarrassed because of the itching |
| *Fatigue* | I had to force myself to get out of bed |
| | I had to have a sleep during the day |
| | Fatigue interfered with my daily routine |
| | I felt worn out |
| | I felt so tired, I had to force myself to do the things |
| | I needed to do I felt so tired, I had to go to bed earlier than usual |
| | Fatigue just suddenly hit me |
| | PBC drained every ounce of energy out of me |
| | Some days it took me a long time to do anything |
| | If I was busy one day I needed at least another day to recover |
| | I had to pace myself for day-to-day things |
| *Cognition* | I had to make a lot of effort to remember things |
| | I had difficulty remembering things from one day to the next |
| | My concentration span was short because of PBC |
| | I had difficulty keeping up with conversations |
| | I found it difficult to concentrate on anything |
| | I found it difficult to remember what I wanted to do |
| *Social* | My sex life has been affected by having PBC |

| | |
|---|---|
| | I feel I neglect my family because of having PBC |
| | I feel guilty that I can't do what I used to do because of having PBC |
| | I sometimes feel frustrated that I can't go out and enjoy myself |
| | I tend to keep the fact that I have PBC to myself |
| | I can't plan holidays because of having PBC |
| | My social life has almost stopped |
| | Everything in my life is affected by PBC |
| | PBC has reduced the quality of my life |
| | I can still lead a normal life, despite having PBC |
| *Emotional* | Because of PBC, I get more stressed about things than I used to |
| | Having PBC gets me down |
| | I worry about how my PBC will be in the future |

Subsequent studies have defined score ranges for each domain, scaling the results in "none", "mild", "moderate" and "severe". Clinical significance of symptoms was also assessed, being defined as moderate and severe manifestations (Table 2) (61).

**Table 2. Stratification of severity of PBC-40 questionnaire domains.**

| PBC-40 domain | None | Mild | Moderate | Severe |
|---|---|---|---|---|
| *General symptoms* | < 7 | 8 - 18 | 19 - 25 | > 26 |
| *Itch* | < 3 | 4 - 8 | 9 - 11 | > 12 |
| *Fatigue* | < 11 | 12 - 28 | 29 - 39 | > 40 |
| *Cognitive* | < 6 | 7 - 15 | 16 - 21 | > 22 |
| *Social and emotional* | < 13 | 14 - 34 | 35 - 49 | > 50 |

Adapted from Newton JL, Hudson M, Tachtatzis P, Sutcliffe K, Pairman J, Burt JA, Jones DE. Population prevalence and symptom associations of autonomic dysfunction in primary biliary cirrhosis. Hepatology. 2007 Jun;45(6):1496-505.

## 5-D itch Scale

Four years later another questionnaire, focused on itch, was introduced in clinical practice as far as, until then, pruritus assessment was unidimensional, measuring intensity, and did not consider its impact on HrQoL. For this reason, a set of questions regarding pruritus was derived from the Total Neuropathy Scale. After that, a group of 234 patients with chronic pruritus, who had undergone a 6-week

follow period, was administered the 5-D questionnaire; they were subsequently retested after 3 days in order to assess the test-retest reliability. The five selected questions cover the following five variables: duration, degree, direction, disability and distribution; answers are scaled as “improved”, “worsened” and “not changed” (62).

**5-D Itch Scale questions:**

1. **Duration**: *During the last 2 weeks, how many hours a day have you been itching?* (1) Less than 6hrs/day; (2) 6-12 hrs/day; (3) 12-18 hrs/day; (4) 18-23 hrs/day; (5) All day.
2. **Degree**: *Please rate the intensity of your itching over the past 2 weeks:* (1) Not present; (2) Mild; (3) Moderate; (4) Severe; (5) Unbearable.
3. **Direction**: *Over the past 2 weeks has your itching gotten better or worse compared to the previous month?* (1) Completely; (2) Much better, but still present; (3) Little bit better, but still present; (4) Unchanged; (5) Getting worse.
4. **Disability**: *Rate the impact of your itching on the following activities over the last 2 weeks*:
    a. Sleep: (1) Never affects sleep; (2) Occasionally delays falling asleep; (3) Frequently delays falling asleep; (4) Delays falling asleep and occasionally wakes me up at night; (5) Delays falling asleep and frequently wakes me up at nights.
    b. Leisure/social: N/A; (1) never affects this activity; (2) rarely affects this activity; (3) Occasionally affects this activity; (4) Frequently affects this activity; (5) Always affects this activity.
    c. Houseworks/Errands: N/A; (1) never affects this activity; (2) rarely affects this activity; (3) Occasionally affects this activity; (4) Frequently affects this activity; (5) Always affects this activity.
    d. Work/School: N/A; (1) never affects this activity; (2) rarely affects this activity; (3) Occasionally affects this activity; (4) Frequently affects this activity; (5) Always affects this activity.
5. **Distribution**: Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically. Head/Scalp, Face, Chest, Abdomen, Back, Buttocks, Thighs, Lower legs, Soles, Palms, Tops of Hands/Fingers,

Forearms, Upper Arms Points of Contact w/ Clothing (e.g waistband, undergarment), Groin, Tops of Feet/Toes.

## Visual Analogue Scale (VAS)

VAS represents the most ancient tool used for the determination of severity of symptoms, as it was firstly introduced in clinical practice in 1921. Subsequent studies, throughout the years have validated its usefulness and its reliability in patients with chronic pruritus.

VAS is an easy-to-use graphical tool, 10 cm long, anchored by a left end "no symptoms" and a right end "worst imaginable symptom". Patients have to draw a line in correspondence of the intensity of the pruritus (63) (Figure 1).

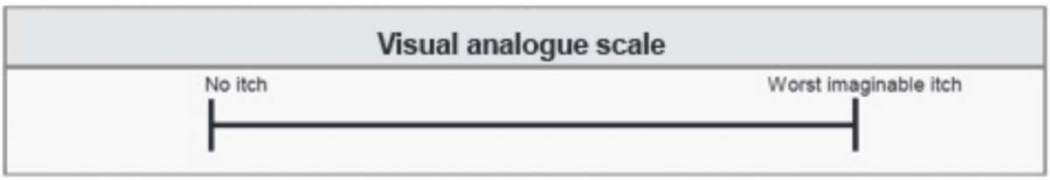



**Figure 1. Visual Analogue Scale of pruritus. Adapted from Phan NQ et al. Acta Derm Venereol. 2012;92(5):502–7.**

## Fatigue Impact Scale (FIS)

FIS was developed in 2014 to assess the impact of fatigue on HrQoL. It includes questions about the perceived impact of fatigue on cognitive (10 items), physical (10) and psychosocial (20) functioning (64,65). Answers are scaled from 0 (i.e., no problems) to 4 (i.e., extreme problem) points, with a maximum score of 160 points (Table 3).

**Table 3. Fatigue Impact Scale (FIS) questions.**

| ***Domain*** | ***Question*** |
|---|---|
| *Cognitive dimension* | I feel less alert (1) |
| | I have difficulty paying attention for a long period (5) |
| | I feel like I cannot think clearly (6) |
| | I find that I am more forgetful (11) |
| | I find it difficult to make decisions (18) |

| | |
|---|---|
| *Because of my fatigue:* | I am less motivated to do anything that requires thinking (21) |
| | I am less able to finish tasks that require thinking (26) |
| | I find it difficult to organize my thoughts when I am doing things at home or at work (30) |
| | I feel slowed down in my thinking (34) |
| | I find it hard to concentrate (35) |
| | I had to force myself to get out of bed |
| | I had to have a sleep during the day |
| | Fatigue interfered with my daily routine |
| | I felt worn out |
| | I felt so tired, I had to force myself to do the things |
| *Physical dimension* | I am more clumsy and uncoordinated (10) |
| | I have to be careful about pacing my physical activities (13) |
| | I am less motivated to do anything that requires physical effort (14) |
| *Because of my fatigue:* | I have trouble maintaining physical effort for long periods (17) |
| | my muscles feel much weaker than they should (23) |
| | my physical discomfort is increased (24) |
| | I am less able to complete tasks that require physical effort (31) |
| | I worry about how I look to other people (32) |
| | I have to limit my physical activities (37) |
| | I require more frequent or longer periods of rest (38) |
| *Social dimension* | I feel that I am more isolated from social contact (2) |
| | I have to reduce my workload or responsibilities (3) |
| | I am more moody (4) |
| *Because of my fatigue:* | I work less effectively (this applies to work inside or outside the home) (7) |
| | I have to rely more on others to help me or do things for me (8) |
| | I am more irritable and more easily angered (12) |
| | I am less motivated to engage in social activities (15) |
| | I have few social contacts outside of my own home (19) |
| | normal day-to-day events are stressful for me (20) |
| | I avoid situations that are stressful for me (22) |
| | I have difficulty dealing with anything new (25) |

| |
|---|
| I feel unable to meet the demands that people place on me (27) |
| I am less able to provide financial support for myself and my family (28) |
| I engage in less sexual activity (29) |
| I am less able to deal with emotional issues (33) |
| I have difficulty participating fully in family activities (36) |
| I am not able to provide as much emotional support to my family as I should (39) |
| minor difficulties seem like major difficulties (40) |
| I have difficulty planning activities ahead of time (9) |
| my ability to travel outside my home is limited (16) |

## EuroQoL 5D-5L (EQ-5D-5L)

EQ-5D-5L was elaborated in 2010 as an improvement of the previous EQ-5D-3L, characterized by a significant ceiling effect. Both questionnaires are composed of five questions concerning mobility, self-care, usual activities, pain/discomfort and anxiety or depression (66). Five answers (3 in the former version) are allowed: "no problems" (L1), "slight problems" (L2), "moderate problems" (L3), "severe problems" (L4) and "extremely severe problems" (L5) (67).

**Mobility**: (1) I have no problems in walking about; (2) I have slight problems in walking about; (3) I have moderate problems in walking about; (4) I have severe problems in walking about; (5) I am unable to walk about.

**Self-care**: (1) I have no problems washing or dressing myself; (2) I have slight problems washing or dressing myself; (3) I have moderate problems washing or dressing myself; (4) I have severe problems washing or dressing myself; (5) I am unable to wash or dress myself.

**Usual activities** (e.g., work, study, housework, family or leisure activities): (1) I have no problems doing my usual activities; (2) I have slight problems doing my usual activities; (3) I have moderate problems doing my usual activities; (4) I have severe problems

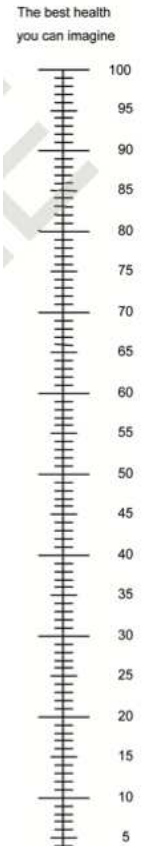



**Figure 2. EuroQoL scale.**

doing my usual activities; (5) I am unable to do my usual activities.

**Pain/Discomfort**: (1) I have no pain or discomfort; (2) I have slight pain or discomfort; (3) I have moderate pain or discomfort; (4) I have severe pain or discomfort; (5) I have extreme pain or discomfort.

**Anxiety/Depression**: (1) I am not anxious or depressed; (2) I am slightly anxious or depressed; (3) I am moderately anxious or depressed; (4) I am severely anxious or depressed; (5) I am extremely anxious or depressed.

We would like to know how good or bad your health is TODAY. This scale is numbered from 0 to 100. 100 means the best health you can imagine. 0 means the worst health you can imagine. Mark an X on the scale to indicate how your health is TODAY. Now, please write the number you marked on the scale in the box below.

## Characterization of disease according to symptoms

The use of the questionnaires described so far allows a better characterization of the disease. Baseline evaluation of fatigue, for example, appears to be an interesting predictor of outcome: higher severity of symptoms are more likely to be found in those who die for decompensation of the liver disease or undergo liver transplantation (43). A study conducted by Jones *et al.* in 2006 (68), observed that fatigue patterns do not change throughout the natural history of disease and its presence is associated with increased risk of any cause, including cardiovascular events. In non-transplanted subjects surviving to a four-year follow-up, fatigue assessed by FIS did not change. Interestingly, no effect of UDCA at optimal dosage on fatigue has been documented. Patients who died of any cause during follow-up had higher scores (> 40) in FIS questionnaire (71% vs. 29%, p=0.005). It has to be said, although, that the subsequent studies (43) did not confirm such an observation, stating that fatigue appears not to be an overall mortality predictor as it is not associated with non-liver-related mortality.

Pruritus, on the other hand, tends to resolve as the disease progresses (50). Moreover, this symptom appears to be more severe in those patients presenting with ductopenic variant of PBC (69), a presentation known for its progressive icteric cholestasis and absence of response to UDCA (70). In contrast to OCA, UDCA does not worsen, nor improves, pruritus (2).

Generally speaking, those patients who present fatigue or itch at the time of

diagnosis are more likely not to respond to UDCA and are more keen on to progressive and rapid progression of disease (70).
A detailed description of current therapeutic strategies for PBC symptoms is reported below.

# Diagnosis

For the diagnosis of PBC 2 out of the 3 following criteria need to be met:

1. Chronic cholestatic liver biochemical test elevation assessed as alkaline phosphatase (ALP) ≥ 1.5xULN (upper limit of normal).
2. Serum AMA or disease-specific ANA positivity.
3. Liver biopsy consistent with PBC.

## Biochemical Tests

Chronic (duration ≥ 6 months) cholestasis often appears to be asymptomatic, for months or years, in early phases; elevation of ALP or GGT, and subsequently conjugated bilirubin, can be early biochemical markers of disease. Howbeit, those markers are not specific: rapid bone growth (in children, Paget's disease, and bone metastasis), vitamin D deficiency and pregnancy can lead to increased levels of ALP. In clinical practice, a simultaneous elevation of ALP, GGT and/or conjugated bilirubin is considered to be driven by cholestatic disease (2).
Serum aminotransferases (i.e., AST and ALT) are rarely markedly elevated and, if present, this suggests an overlap syndrome with Autoimmune hepatitis (AIH). When elevated, AST and ALT, along with IgG, reflect the grade of periportal and lobular necrosis and inflammation.
Elevated levels of serum bilirubin (71) associated with low albumin and prolonged prothrombin time (INR) are typical of advanced stages of disease and are ascribable to ductopenia and biliary piecemeal necrosis (72).

## Autoantibodies

As far as an elevation of ALP or any other biochemical marker is not specific, it is necessary to detect specific antibodies: AMA or PBC-specific ANA (sp100 and gp210) in peripheral blood. There are different tests that can be employed, such as indirect immunofluorescence (detects 90-95% of PBC patients), immunoblotting

and enzyme-linked immunosorbent assay (ELISA); the last two tests have sensitivity and specificity rates that are above 95% (1).

It must be understood that AMA are not specific for PBC, the prevalence of those antibodies in general population is up to 0.1%, whilst the prevalence of disease is much lower (0.04%); this meaning that AMA testing has to be targeted to specific subject, for whom the disease is highly suspected (73).

## Liver Biopsy

A liver biopsy is required in (74):

1. AMA-negative patients with unexplained chronic cholestasis (10% of PBC people). In these cases, liver biopsy allows the differentiation among PBC, small ducts variant of Primary Sclerosing Cholangitis (PSC) and hepatic sarcoidosis.
2. Patients with suspected Overlap Syndromes, which may benefit from immunosuppressive therapy. Interface hepatitis is present in both diseases presenting in "pure variants" of PBC as biliary piecemeal necrosis, while in AIH-PBC overlap as lymphocytic piecemeal necrosis.
3. PBC people suspicious for another diagnosis, *i.e.*, non-alcoholic steato-hepatitis (NASH).

An adequate sampling should provide at least 10-15 portal fields (75), including periportal/periseptal copper deposition, periportal/periseptal feathery degeneration with or without Mallory-Denk bodies, and cholestatic rosettes.

As mentioned before, PBC is characterized by chronic non-suppurative cholangitis that affects specifically interlobular and septal bile ducts, determining the so-called "florid duct lesions".

## Role of Imaging

PBC does not cause any alteration of liver parenchyma and biliary tract. Nevertheless, ultrasound (US) represents a first line non-invasive tool to be used to differentiate intra- and extrahepatic forms of cholestasis (1) and to monitor the development of signs of cirrhosis, decompensation and/or malignancies (*i.e.,* hepatocellular carcinoma).

Subsequently, magnetic resonance cholangiopancreatography (MRCP), plays an important role in excluding biliary obstructions that may cause cholestatic liver

tests elevations, and allows the differential diagnosis with small duct variant of PSC. Moreover, a significant number of PBC people present characteristic alterations at MRI and CT such as the so-called “halo sign” (i.e. T1- and T2-weighted hypodensity centred around portal venous branches) (76) and stable periportal adenopathy.

Vibration-controlled transient elastography (VCTE) has become, in the last decade, a powerful non-invasive surrogate marker of liver fibrosis and progression to cirrhosis (77). Values of liver stiffness measurements (LSM) ≥ 9.5 kPa have been associated with a 5-fold increase in risk of liver decompensation, OLTx and death (72). Even though there are no established LSM thresholds or time points for performing VCTE, EASL strongly recommends the use of non-invasive LSM during follow-up of PBC people (78), also in light of the fact that LSM can be used as surrogate marker of disease progression (2). Baseline evaluation of liver fibrosis with TE is strongly recommended by current guidelines, in order to discriminate advanced disease stage (78).

# Therapy

There are two pillars in treatment of PBC:

1. Preventing the development of end-stage liver disease (*i.e.* decompensated cirrhosis and/or malignancies).
2. Control of symptoms, such as cholestatic pruritus, fatigue and social isolation (79).

Over the last decades, different therapies have been attempted, testing different targets, which are supposed to be crucial in the development of the disease.

## Ursodeoxycholic acid (UDCA)

UDCA is a hydrophilic bile acid physiologically present in human bile, accounting for 4% of total bile acids (80). Its first use dates to Chinese traditional medicine (618 AD), when it was administered to patients who had liver problems. It was not until the ‘80s of the last century that UDCA was employed for the treatment of cholestatic liver disorders such as PBC, PSC, intrahepatic cholestasis of pregnancy (ICP) and other adult and infant cholestatic disease.

Once ingested, UDCA reaches the proximal jejunum and it is absorbed in its unconjugated form by passive non-ionic diffusion, finally reaches the liver and is

conjugated with glycine or taurine. After that, it is secreted into bile and in the small intestine lumen. UDCA conjugated form is considered to be the active form in treatment of cholestasis; it is responsible for the stimulation of biliary secretion of bile acids by hepatocytes and, in a long-term setting, decreases circulating concentration of bilirubin and other hydrophobic acids and acts over transcription of transporters, both during and after the process. Moreover, UDCA protects cholangiocytes against damage produced by inflammation and toxic hydrophobic bile acids and stimulates the secretion of HCO3- by cholangiocytes, the so called " bicarbonate umbrella" (79). Beneficial effects of UDCA have been proved also on ileocytes and monocytes.

Different meta-analyses have shown the benefits of the administration of UDCA in people with PBC. In particular, it has been demonstrated by different randomized controlled trials and metanalyses that the usage of UDCA at a daily dose of 13-15 mg/kg is safe and is associated with a significant reduction of liver biochemistry (81–83). Moreover, UDCA is capable of slowing down the progression of disease in patients without evidence of fibrosis (stage 1-2) at the time of diagnosis (79).

Before the introduction of UDCA in clinical practice, 49% of people with PBC progressed to cirrhosis; nowadays it only happens in a 13% of long-term users (84), with 10-year survival that is slightly lower than that of an age- and gender-matched general population (85). It should be taken into account that UDCA, administered in advanced-stage disease, despite its beneficial effect on biochemistry, is not able to prevent the development of malignancies (namely HCC) (86).

UDCA is administered orally, one or multiple doses, is generally safe and well tolerated. However, some possible side effects are reported including diarrhoea and flatulence [scheda tecnica UDCA], more rarely weight gain in the first year of therapy, hair loss (79). Finally, UDCA administration is safe even during pregnancy and breastfeeding.

## Obeticholic acid (OCA)

Obeticholic acid (OCA) is a selective Farnesoid X receptor (FXR) agonist, which has a 100 times greater potency in activating FXR nuclear signalling than the natural ligand (chenodeoxycholic acid), resulting in an overall protection of hepatocytes against bile acid toxicity (87). In order to do so it suppresses *de novo* synthesis of bile acids, promotes choleresis, by targeting two enzymes in the human

liver, the CYP7A1, which is downregulated, provoking a reduction of the conversion of cholesterol into bile acids and FGF19, which strengthens the suppression (37).

OCA was conditionally approved by FDA in 2016, based on the results of the phase III trial (POISE). This trial showed the efficacy of OCA in patients who were non-responders or intolerant to UDCA, who represent up to 40% of PBC people (88), varying on the criteria used for the assessment (89).

OCA can be administered in all patients who show intolerance or with inadequate response after 12 months of UDCA therapy, defined as ALP ≥ 1.5xULN and/or bilirubin > 1 and < 2xULN. Starting dose should be 5 mg per day, with dose titration up to 10 mg after 6 months of treatment, according to response to therapy and tolerability (2).

Cirrhotic patients deserve special attention as far as OCA has shown a limited safety profile in this population. In Child-Pugh A patients, OCA can be used as in non-cirrhotic patients but is contraindicated in patients with previous episode of decompensation, current decompensation or development of progression in the Child-Pugh status during follow-up.

OCA presents different adverse effects that can cause discontinuation of the therapy. The most common, as assessed by different trials and by the regulatory agencies (i.e., EMA and AIFA), is pruritus; it can appear or worsen after OCA introduction. Other side effects include abdominal discomfort and thyroid alterations (common), decompensation of cirrhosis (very rare) [Scheda tecnica OCA].

**POISE trial**

The pivotal phase 3 placebo-controlled trial that allowed the introduction of OCA in clinical practice dates back to 2013 and involved 217 subjects with insufficient response or intolerance to first-line therapy with UDCA, demonstrating efficacy in reducing liver biochemistry tests and progression to end-stage liver disease.

Entry criteria included ALP level ≥1.67xULN or an abnormal total bilirubin level (< 2xULN). After inclusion, patients were randomly assigned to three groups, who daily received: placebo, 5 mg of OCA (then titrated to 10 mg) and 10 mg of OCA, respectively.

Primary endpoints were ALP reduction < 1.6xULN, with a reduction of at least

15% from baseline and a normalization of total bilirubin at 12 months. Secondary endpoints meant to explore the effect of OCA on ALP, GGT, AST, ALT, total and conjugated bilirubin, albumin, INR, FGF-19, plasma bile acids, CRP, TNF-a, IL-6, TGF-b, CK-18, liver stiffness and symptoms (assessed with Visual Analogue Scale and PBC-40 questionnaire). Exploratory endpoints were the evaluation of IgA, IgM, IL-12, IL-23. VAS and 5-D pruritus questionnaires were used in order to evaluate the safety and side effects of the drug.

After 12 months of treatment, people treated with OCA, both at 5-10 mg and 10 mg daily doses, reached higher primary endpoints rates than placebo group (46%, 47% and 10%, respectively). The response was rapid, with significant differences between treated and non-treated patients after 2 weeks of therapy. Also, secondary endpoints were met much more frequently in treated groups. In the POISE trial, OCA did not result in a significant reduction of symptoms as measured by the PBC-40 questionnaire, on the contrary, patients included in the 10 mg – arm showed significantly worse scores. Pruritus was the most frequently reported adverse event, with a higher incidence reported among patients in 5-10 mg and 10 mg arms compared to patients taking placebo (56%, 68% and 38% respectively, $p<0.001$). Eight (4%) people (7 from 10 mg arm and 1 from 5-10 mg group) withdrew the experimentation do to intolerable pruritus. Modifications in pruritus intensity, assessed with Visual Analogue Scale (VAS) of pruritus and 5-D questionnaire, were greater in 10-mg group than placebo one (VAS: $p<0.001$ at week 2, $p=0.003$ at month 3, $p=0.03$ at month 6; 5D Scale: $p<0.001$ at week 2, $p=0.005$ at month 3). After 12 months of treatment no significant difference in Visual Analogue Scale (VAS) of pruritus was observed between treated and placebo groups; thus suggesting that pruritus is a very early adverse event that can reach stabilization during follow-up. Among all patients requiring appropriate treatment for pruritus, mainly bile acid sequestrants, there was no difference regarding the study arm belonging.

The open label extension study evaluated the long-term efficacy of OCA, substantially confirming the beneficial effect of the drug on liver biochemistry. More in detail, an ALP reduction was observed at every annual timepoint; total and direct bilirubin were stabilized, with significant reduction at 12 months. Fatigue and pruritus were confirmed as the most common adverse effects of OCA treatment. Pruritus, as assessed with VAS score, showed a transient increase at 3 months of

treatment, with subsequent return to baseline in the following months (90).
Notably, in both studies, there were no cirrhotic patients, the great majority of patients were women and were taking UDCA therapy.

**Real world experiences**

Throughout the years that followed the introduction in clinical practice of OCA four different real-world studies have been published, in different geographical settings, namely Italy, Canada and Iberian Peninsula.
The first published was the study from Roberts et al that described a Canadian cohort (91) including 64 patients with insufficient response to UDCA with at least 12 months follow-up. Primary outcomes were considered a modification of ALP, GGT and total bilirubin; while secondary outcomes included changes in AST, ALT, IgM, platelets, albumin and matching with POISE primary outcomes (see above). This study showed a significant reduction of ALP; observed within the first three months from starting OCA with a subsequent stabilization between month 3 and 12. Also GGT decreased, while total bilirubin remained unchanged. Transaminases and IgG diminished, while albumin and platelet count remained stable. All those results were much more consistent in POISE-eligible patients, in comparison with those who were not. Interestingly, patients with advanced stage (14%), defined as LMS ≥16.9 kPa, showed lower levels of ALP at initiation and confirmed a significant reduction of ALP after OCA introduction. In addition to pruritus, other reported side effects of OCA therapy were gastrointestinal toxicity (*i.e.*, nausea, constipation, bloating), suspected hepatotoxicity, polymenorrhagia, headache and skin rash.
Subsequently the Italian PBC study group reported about a multicentric cohort including 191 patients from 38 Italian centres, who had taken at least 1 dose of OCA and 12 months of follow-up after OCA introduction. Primary study endpoint was a biochemical response at 6 and 12 months assessed as per POISE criteria (ALP < 1.67xULN with a reduction >15% compared to baseline and normal levels of TB) (92). Secondary endpoint was the normalization at 12 months of ALP, ALT, and TB. A systematic evaluation of pruritus was also performed. In this study, patients with cirrhosis and/or overlap syndrome were also included. After 6 and 12 months after the first dose, 34% and 42.9% of patients matched POISE criteria; at

mentioned time points, 4.7% and 11% of patients reached secondary endpoints. No significant differences in biochemical response were observed in cirrhotic patients compared to non-cirrhotic. Discontinuation of therapy was observed in 17% of patients, in half of the cases during the first six months. Sixty six percent of discontinuations were due to new-onset or worsening of pruritus, 9.1% to worsening of liver function, other rarer reported causes were anaemia, headache, and myalgia. Pruritus was the most common side effect (52 patients, 27.3%): 40 patients had de novo pruritus and 12 had worsening of pre-existing pruritus.

Univariate statistical analysis showed that age at PBC diagnosis and at OCA start, liver cirrhosis, OCA started after fibrates, pre-treatment values of ALP/ULN, AST/ULN, GGT/ULN, and of total bilirubin were significant predictors of OCA treatment failure.

A subsequent analysis of the Italian PBC study group including 100 patients with PBC in cirrhotic stage (93) showed that male sex, history of ascites, albumin levels, Child-Pugh score, MELD score, ALP/ULN, GGT/ULN, ALT/ULN, AST/ULN and total bilirubin, are significantly associated with a reduced probability of biochemical response to OCA therapy according to Poise criteria. Moreover, total bilirubin $\geq$ 1.4 mg/dl was found to be the most accurate chemical predictor of serious hepatic adverse events (SAEs), showing high specificity (88%), NPV (96%) but limited PPV (35%). According to this observation, administering OCA to cirrhotic subjects with total bilirubin above this cut-off is not advisable for the risk of developing hepatic SAE, while if under mentioned cut-off OCA usage is considered safe.

Gomez *et al.* (94) conducted an open label, prospective, real-world, multicentric study in which 120 subjects were enrolled and 78 of them had at least 12 months of follow-up. ALP, AST, and ALT demonstrated a significant reduction over the study period, 29.5% (n=23) of patients matched with POISE criteria of response, with albumin levels being the only significant predictor of response. No significant changes were assessed for IgG, IgM, and surrogate markers of fibrosis; nevertheless, patients treated with OCA, experienced a stabilization of liver stiffness measurement.

## Off-label therapies

### Fibrates

Fibrates are worldwide used antilipidemic drugs, thanks to their activity on PPAR pathway. The interaction among fibric acids and each of the PPAR isoforms has beneficial effects on inflammation, fibrosis and cholestasis, through the increasing of the secretion of phosphatidylcholine (88).

For this reason, a double blind, placebo-controlled, phase 3 trial with bezafibrate 400 mg/day + UDCA vs. placebo + UDCA, the BEZURSO trial, was conducted in France (95). This study considers a stricter endpoint than that used in the POISE study, in fact the French study defined as primary endpoint the complete normalization of ALP, transaminases, total bilirubin, albumin and INR. The endpoint was met in 30% of patients treated with bezafibrate and in 0% of patients treated with placebo (56). Interestingly in this trial, patients treated with bezafibrate showed a relevant reduction of pruritus and fatigue. Moreover, variations from baseline to 24 months in itch intensity score between bezafibrate and placebo groups reached -95% [-241%; 50%]; fatigue reduction was observed in 30% of patients treated with Bezafibrates vs. 19% in placebo group.

Furthermore, the triple therapy of OCA + UDCA + fibrate (Bezafibrate or Fenofibrate) in patients with inadequate response to dual therapy has been also investigated in a multicentric retrospective study(58), and has shown promising results obtaining a more significant reduction of ALP levels than double therapy. More recently, the results of a phase 2 double blind trial to test safety and effectiveness of OCA + bezafibrate in patients with insufficient response to UDCA were presented at the International Liver Congress 2023 held in Vienna (Nevens et al, oral communication FRI-23 OS-046).

It must be noted, however, that fibrates are also known for possibly increasing transaminases, bilirubin and creatinine values, raising concern for people affected by a chronic liver disease and for this reason if such therapies are initiated an appropriate monitoring of transaminases, bilirubin and serum creatinine is strictly advisable.

**Budesonide**

Budesonide is a synthetic corticosteroid which is characterized by a high first-pass metabolism within the liver, for this reason it has less systemic side effects than prednisolone. Nevertheless, this drug has deleterious outcomes in patients with advanced stage liver disease (*i.e.*, portal hypertension and cirrhosis).

In 1999 a randomized placebo-controlled trial was conducted and an improvement of biochemistry, histology grade and fibrosis were documented; however, Mayo PBC score prognostic index and bone mineral density were significantly increased (100).

Due to said side effects and the results from the phase III trial, prematurely interrupted, that did not meet the primary endpoint, Budesonide is not considered a second line treatment for PBC but can be considered in patients with inadequate response to UDCA and significant inflammation documented on liver biopsy.

## Assessment of inadequate response to therapy

Careful evaluation of response to treatment is fundamental for different reasons: initiating a second-line or experimental therapy, assessing the prognosis of the patient, or beginning liver transplant evaluation.

For this purpose, different strategies have been attempted throughout the years, the most promising ones considering standard serum liver tests and more recently LSM in combination with scoring systems (101). Biochemical response can be evaluated both with qualitative binary definitions or continuous scoring systems (2).

### Qualitative binary definitions of response to UDCA

Different retrospective, often single centre, studies have attempted to establish definitions of the biochemical response to UDCA. These include the following definition (Table 4)

**Table 4. Internationally validated response criteria to PBC therapy.**

| Name | Timepoint (months) | Treatment failure | Ref. |
|---|---|---|---|
| **Barcelona** | 12 | ΔALP < 40% and ALP ≥ 1xULN | (86) |
| **Rotterdam** | 12 | TB ≥ 1x ULN and/or albumin > 1 mg/dl | (102) |
| **Toronto** | 24 | ALP ≥ 1.67x ULN | (103) |
| **Paris-II** | 12 | ALP ≥ 1.5x ULN<br>or AST ≥ 1.5x ULN<br>or TB > 1 mg/dl | (104) |
| **Mayo** | 6 | ALP ≥ 2x ULN | (105) |

Although the largest part of the scoring systems has been validated on a 12-month timespan, a 14-year cohort study conducted by Zhang *et al.* has shown that the

assessment of response to UDCA therapy, with the criteria published so far, at 12 months is as reliable as at 6 months (89).

### Continuous scoring systems

The prognostic tools discussed above, even if easy to use in clinical practice, present several limitations such as the loss of predictive pieces of information (e.g., markers of disease stage). For this reason many efforts have been spent in order to validate new scoring systems that could incorporate both measurements based on biochemistry levels and parameters of disease severity (106).
With these purposes GLOBE score (106) and UK-PBC (107) score were developed, showing better performances in predicting death or liver transplantation.
GLOBE score was validated in 2015 in a cohort of 2488 subjects with a median follow-up of 7.8 years that showed transplant-free survival rates at 5, 10 and 15 of 90.0%, 77.5% and 65.6% respectively (106). The score considers age, bilirubin, albumin, ALP, and platelet count as univariate Cox regression analyses showed them to be associated with higher risk of liver transplantation or death.
UK-PBC Risk Score, on the other hand, evaluates baseline albumin and platelet count, as well as bilirubin, AST, ALT and ALP after 12 months of treatment with UDCA (107).

## Treatment of AIH-PBC overlap syndromes.

Almost 10% of PBC patients present with additional features of autoimmune hepatitis (AIH); as previously discussed, these cases deserve the execution of a liver biopsy to determine the diagnosis. Immunosuppressive treatment, in addition to UDCA, is mandatory in those patients presenting with severe interface hepatitis, while it can be considered in those with moderate one (108). Moreover, AIH-PBC patients present worse prognosis and more severe fibrosis grade than those with PBC alone (109).

## Management of symptoms

### Pruritus

Pruritus is one of the most burdensome symptoms in PBC3 and, for this reason, need to be promptly recognized and treated according different possible therapeutic options (Figure 3). Bile sequestrants (namely cholestyramine) are the most widely

used drugs for the treatment of cholestatic pruritus even if the evidence and efficacy are poor. Moreover, intolerance is frequent and caused by a poor palatability, bloating and sometimes constipation. Furthermore, this medication should be taken 2-4 hours far from UDCA or OCA, as it interferes with their intestinal absorption. Colesevelam, another bile acid-binding resin, has shown better results in reducing serum bile acid levels with minor side effects; nevertheless, a randomized-controlled trial has shown that this drug is not more effective than placebo in reducing pruritus.

Rifampicin, an anti-tuberculotic drug, can be used as second line therapy for cholestatic pruritus at a starting dose of 150 mg twice daily orally. It should be taken into account, although, that this drug may cause reversible liver injury in up to 15% patients (1) and haemolysis, for this reason periodical blood testing is required (2).

Naltrexone and Nalmefene, oral opiate antagonists are used as third-line therapy thanks to their ability to reduce the sensation of itching. Disadvantages in using these drugs include opiate withdrawal-like reactions and reduction of pain threshold (2).

Lastly, selective serotonin reuptake inhibitors (SSRI, namely sertraline) and gabapentin can be used, if patients are non-responders to all the other therapies.

Of interest, physical approaches such as nasobiliary drainage, molecular absorbance recirculating system (MARS), albumin dialysis and UV light therapy have shown, in limited cases, promising results (2).

Liver transplantation should be considered in all those patients with untreatable pruritus as far as has been proved to be highly effective (110).

The more relevant novelty in the treatment of pruritus in PBC comes from the results of the FITCH trial. During this 21-day-long placebo-controlled study, bezafibrate was administered at 400 mg dose to patients affected by PBC, PSC and SSC complaining moderate to severe pruritus (≥ 5/10 on Visual Analogue Scale - VAS). Primary endpoint of the study was a reduction ≥ 50% of the VAS score after 21 days of treatment; mentioned result was observed in 45% of people receiving bezafibrate and 11% of placebo group patients ($p=0.003$, difference = 34%). This reduction was observed both in the measurements in the morning and evening scores ($p<0.001$) (111).

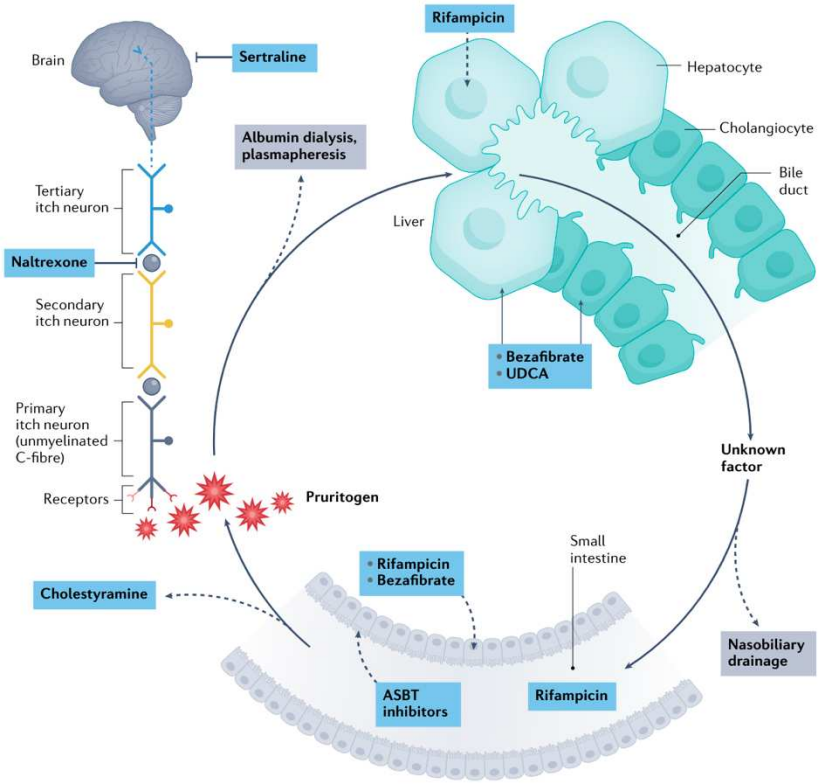



**Figure 3.Potential pruritogens in cholestasis and antipruritic interventions. Adapted from "Beuers U, Wolters F, Oude Elferink RPJ. Nat Rev Gastroenterol Hepatol. 2023 Jan;20(1):26-36."**

## Fatigue

Due to its frequency (over 50% of PBC people) and its significant impact on patients' quality of life fatigue, management and assessment of fatigue needs to be constant and parallel to the treatment of the underlying disease. It is crucial, in this sense, to assess if therapies or concomitant, especially autoimmune, diseases may be the cause or worsening factor of fatigue. The treatment of fatigue rests on two pillars: treatment of PBC disease process itself and specific targeting of symptoms and their pathophysiological mechanism. It has to be considered that both first and second line therapies for PBC do no reduce relative risk of fatigue when compared to control groups (RR=0.86, p=0.19) (112). Interestingly, PBC people who undergo liver transplant experience higher rates of fatigue; albeit OLT does not solve PBC-related fatigue issues, but reduces the additional component related to decompensated cirrhosis (113).

Even if poorly understood this symptom appears to be strongly associated with cognitive dysfunctions (*i.e.*, memory impairment, impaired attention or

concentration and psychomotor disfunction), suggesting a common pathophysiological process (114). Among other hypothesis, cognitive symptoms appear to be associated with impaired cerebral perfusion, that also leads to autonomic dysfunctions such as bradycardia, low blood pressure and orthostatic hypotension (115). A dysfunction of CNS has also been summoned up to explain central fatigue, making that a strong connection in both symptoms pathophysiology (116).

# Complications and management

## Osteoporosis

Osteoporosis is a common complication of PBC, affecting 14-52% of PBC patients (117) and leading to pernicious consequences such as spontaneous fracturing; of interest, cholestatic diseases appear to be a more common aetiology than osteomalacia (*i.e.* defective bone mineralization due to the lack of vitamin D).

In women with PBC the loss of bone mass is twice more rapid than healthy same-aged people. This phenomenon is due to the alteration of the remodelling process of the bone mass as a result of a multitude of factors such as insulin-like growth factor-1 deficiency, hypogonadism, cholestasis, genetic susceptibility such as vitamin D receptor gene polymorphisms, decreased vitamin D levels (117).

As in general population, in patients with stage 1 and 2 PBC older age, postmenopausal status and lower BMI appear to be independent risk factors for osteoporosis; while stage 3 and 4 patients have a significantly lower bone mass than general population (118).

In light of the high risk of bone disease in those patients, DEXA is suggested at diagnosis, as adequate exercise and vitamin D supplementation for preventing the uprising of osteoporosis (2).

## Fat-soluble vitamins deficiency

Vitamins A, D, E and K deficiency is due to reduction of bile acid secretion. It is rare and associated with advanced liver disease and prolonged jaundice (2) but is no more reported.

## Hyperlipidaemia

Alterations in the lipid profile are found in up to 85% of PBC people, with elevation of HDL cholesterol, especially in early-stage disease and a subsequent decrease as PBC progresses. LDL levels, on the other hand, tend to increase as the disease advances. Despite this, an increase in myocardial infarction has not been documented so far (119). For this reason, pharmacological interventions are suggested in those who have other cardiovascular risk factors.

## Varices

Natural course of disease can end up in cirrhosis and, therefore, in the development of portal hypertension. It has to be said, however, that unlike other liver diseases, rarely, portal hypertension can appear also in a pre-cirrhotic stage of PBC as it is frequently associated with the presence of nodular regenerative hyperplasia and obliterative portal venopathy (120).

A platelet count < 140 x10^9 cells/L and/or a Mayo risk score of ≥ 4.5 seem to be reliable indicators of those people deserving screening endoscopy (121).

A study conducted by Bressler et al. (122) showed that platelet count < 200 x10^9 cells/L, serum albumin < 4 g/dl and serum bilirubin ≥ 1.2 mg/dl are independent risk factors for the presence of oesophageal varices.

Management of varices and eventual haemorrhage should be done following Baveno-VI guidelines, with administration of beta-blockers in patients with large oesophageal varices, even if it worsens fatigue.

A current study by the Italian PBC study group is now aiming to refine the risk of oesophageal varices by adopting simple non-invasive tests in patient with PBC.

Furthermore, as soon as complications of cirrhosis appear and according to disease severity scores, such as MELD, it is necessary to start evaluation for liver transplant. LT has demonstrated elevated rates of success in treating the disease and its complications such as pruritus; nevertheless, it has to be said that recurrence of PBC (rPBC) is as common as 20% of cases after 10 years (79).

## Hepatocellular carcinoma

Even if rare, HCC is the most dreaded complication of PBC. Its incidence is estimated at 0.34 per 100-person year in the PBC population. Risk factors for the development of HCC appear to be male sex (HR 2.91, $p<0.0001$), advanced disease stage, thrombocytopenia and hepatic decompensation (122). Absence of treatment

is not a risk factor by itself; but non-response criteria (Paris-I, Paris-II, Rotterdam, and Toronto criteria), are able to predict the future risk of developing malignancy. EASL recommends regular screening for HCC in cirrhotic patients with cross-sectional imaging every six months, with or without the measurement of alpha fetoprotein (AFP) (2).

# Confidence in treatment

Clinical presentation of the disease and its complications are not the only concerns of patients, also the awareness of the unpredictability and chronic nature of their condition are matters of burden. Several studies have demonstrated that confidence in treatment and patients' trust are determinants of adherence to treatment and overall management outcome.

A pivotal transnational study conducted by Wunsch *et al.* in early 2023 has assessed adherence to treatment and overall outcome in a cohort of 1178 subjects affected by autoimmune liver diseases (*i.e.*, PBC, PSC and AIH) who accepted to fill in an online questionnaire regarding their general quality of life (EQ-5D-5L and EQ VAS, SSS-8) and their mental health (GAD-2 and PHQ-2).

The study showed that in all the three diseases the quality of life in reduced and the reduction is more relevant in PBC patients where relevant depression was observed in 17% of patients.

The multivariate analysis conducted on the data set showed that treatment confidence is a common, and potentially, modifiable factor and, in addition to that, depression has been seen to be a key determinant of significant impairment of HrQoL and lower confidence in their treatment. On the other hand, female gender, younger age, and unknown disease stage were unmodifiable determinants of poor HrQoL. In PBC people, management in a transplant centre and treatment with UDCA appear to be enhancing factors of treatment confidence (123).

It has to be said, although, that a mismatch between patients' perspectives and objective disease parameters has been documented by de Veer et al. (124). In this study, 178 patients were presented with five questions regarding: treatment status, need for additional therapy and expected prognosis in comparison to their peers. The vast majority of interviewed people reported a reduced life expectancy span; interestingly, GLOBE score (where available) proved a normal prognosis for 65%

of the patients.

Finally, an Italian study lead by our group and including more than 200 patients with PBC from 7 tertiary Italian centres showed the key role played by the promotion of timely referral to the specialist and the facilitation of the communication between healthcare professionals and patients (125). In this study 210 patients were administered a specific questionnaire in order to assess patient's past history, symptoms and their impact on the quality of life, follow-up, treatment and perceived satisfaction of patients toward the provided care. A series of symptoms was registered including fatigue, pruritus and sicca syndrome; within 18 months 68% of them received a diagnosis of PBC. People included in the study showed concern about

possible health problems or the negative impact of mentioned symptoms on their life. The vast majority of them were satisfied with efficacy and tolerability of treatment, however almost a quarter of them needed an improvement in the relationship with the specialist and more information on the disease.

# Aim of the study

To date, no data from clinical trials or real-life cohorts exists on the effect of obeticholic acid on health-related quality of life (HrQoL) and illness perception together with symptoms and biochemistry. For this reason, we designed a phase 4 real-life observational trial that aimed to assess the impact of OCA not only on patients' biochemistry and liver stiffness but also in symptoms, HrQoL and illness perception.

# Materials and Methods

We designed a phase 4 observational open label study, approved by the local Ethical Committee (AOP 1515) in which we included PBC patients older than 18 years with insufficient response to UDCA therapy that started add-on therapy with OCA who agree to participate in this study. Patients were given OCA if they met the Italian Medicine Agency (AIFA) prescription indications: *i.e.* ALP > 1.5 x ULN or total bilirubin > 1 x ULN and < 2xULN after 12 months from starting UDCA or intolerant to UDCA. Patients were recruited from February 2018 to June 2022. Data lock was established at 28$^{th}$ February 2023.

## Baseline assessment

At the time of the enrollment, information concerning patient's biographical data, medical history, and the PBC-specific data were collected, including:

- Year of birth, gender.
- Year of diagnosis, AMA and PBC-specific ANA positivity, AIH overlap.
- Presence of cirrhosis at diagnosis of PBC and the time of enrollment. Cirrhosis was defined by the histological criteria (if available), the ultrasonographic criteria, the elastographic criteria (LSM by FibroScan > 16.9 KPa) and/or the presence of signs of portal hypertension.
- Presence of AIH overlap syndrome and/or other autoimmune comorbidities (autoimmune thrombocytopenia, autoimmune thyroiditis, Sjögren syndrome, Raynaud phenomenon, vitiligo, scleroderma).
- Concomitant therapies for PBC including UDCA and fibrates.
- Concomitant therapy for pruritus.

Every 6 months from enrollment, according to current indications for OCA treatment, patients were monitored with physical examination, blood lab tests, development of adverse events and clinical outcomes of PBC (cirrhosis development, cirrhosis decompensation…)

Upper abdominal ultrasound and liver stiffness measurement by FibroScan were performed annually, except on cirrhotic patients where ultrasound was performed every 6 months for HCC surveillance.

The following variables were collected at each visit (if available): aspartate aminotransferases (AST), alanine aminotransferases (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (gGT), total bilirubin, direct bilirubin, albumin, platelets, INR, total cholesterol, HDL cholesterol, triglycerides, creatinine, presence of pruritus, adverse events, UDCA and OCA dosage, concomitant therapy, cirrhosis at ultrasound, liver stiffness values, presence of ascites, peripheral edema, flapping tremor and development of esophageal or gastric varices.

# Symptoms assessment

To assess symptoms and their impact on QoL during OCA therapy patients were asked at each visit with an open question their perceived wellbeing status. Moreover, in the week before the planned visit, they were asked to complete the following questionnaires, that were collected at the time of the visit: PBC-40, Fatigue Impact Scale (FIS), 5-D Itch scale, EuroQoL-5D-5L in the Italian version as reported below.

## Scala 5-D

1. **Durata**. Durante le ultime 2 settimane, per quante ore al giorno ha avvertito prurito? (1) Meno di 6 ore al giorno; (2) 6-12 ore/giorno; (3) 12-18 ore/giorno; (4) 18-23 ore/giorno; (5) Tutto il giorno.
2. **Grado**. La preghiamo di valutare l'intensità del prurito nelle ultime 2 settimane. (1) Non presente; (2) Leggero; (3) Moderato; (4) Grave; (5) Insopportabile.
3. **Direzione**. Nelle ultime 2 settimane il prurito è migliorato o peggiorato rispetto al mese precedente? (1) Completamente risolto; (2) Molto meglio ma sempre presente; (3) Leggermente meglio, ma sempre presente; (4) Invariato; (5) Peggiorato.
4. **Invalidità**. La invitiamo a valutare l'impatto del prurito sulle seguenti attività nelle ultime 2 settimane.
    a. Sonno: (1) Non influenza mai il sonno; (2) Occasionalmente ritarda il sonno; (3) Frequentemente ritarda il sonno; (4) Ritarda il sonno e occasionalmente mi sveglia durante la notte; (5) Ritarda il sonno e frequentemente mi sveglia durante la notte

b. Svago/Rapporti sociali: (0) N/D; (1) Non influenza mai questa attività; (2) Raramente influenza questa attività; (3) Occasionalmente influenza questa attività; (4) Frequentemente influenza questa attività; (5) Influenza sempre questa attività.
c. Lavori di casa/ commissioni: (0) N/D; (1) Non influenza mai questa attività; (2) Raramente influenza questa attività; (3) Occasionalmente influenza questa attività; (4) Frequentemente influenza questa attività; (5) Influenza sempre questa attività.
d. Lavoro/Scuola: (0) N/D; (1) Non influenza mai questa attività; (2) Raramente influenza questa attività; (3) Occasionalmente influenza questa attività; (4) Frequentemente influenza questa attività; (5) Influenza sempre questa attività.

5. **Distribuzione**. Indichi se il prurito è stato presente nelle seguenti parti del corpo nelle ultime 2 settimane. Se una parte del corpo non è elencata, selezionarne una adiacente anatomicamente. Testa/Cuoio capelluto, Viso, Torace, Addome, Dorso, Natiche, Cosce, Parte inferiore delle gambe, Parte superiore dei piedi/delle dita, Piante dei piedi, Palmi, Parte superiore delle braccia Punti di contatto con gli abiti: - Cintura, - Indumenti intimi - Altro, Inguine.

## Scala analogica visiva del prurito

**GRAVITÀ:** Tracci una linea nel punto della scala che rappresenta meglio il livello di gravità del prurito (Figure 4):

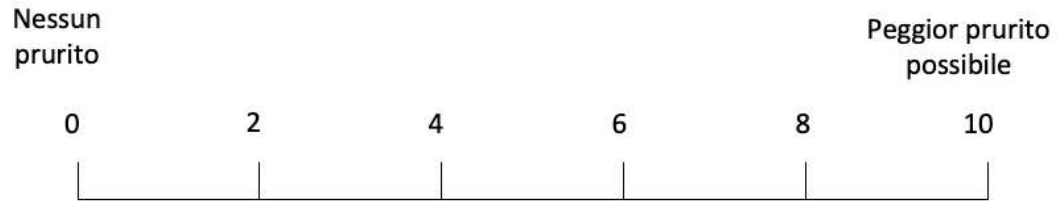



**Figure 4. Visual Analogue Scale (VAS).**

## PBC-40

Per rispondere alle domande seguenti cerchi la risposta che vuole dare, come nell'esempio che segue: Mai, Raramente, Qualche volta, Spesso, Sempre, Non l'ho avuto.

Di seguito trova alcune frasi sulla digestione e sulla dieta. Indichi quanto spesso

ciascuna delle situazioni descritte l'ha riguardata NELLE ULTIME QUATTRO SETTIMANE

1. Sono stato/a in grado di mangiare ciò che volevo
2. Ho mangiato o bevuto poco, ma continuavo a sentirmi gonfio/a
3. Mi sono sentito/1 poco bene quando ho bevuto alcolici
4. Ho avuto dei fastidi sul lato destro del corpo
5. Ho avuto gli occhi secchi
6. Ho avuto la bocca molto secca
7. Ho avuto dei dolori alle ossa delle braccia e delle gambe
8. Il prurito mi ha disturbato il sonno
9. Mi sono grattato/a così tanto da far sanguinare la pelle
10. Ero in imbarazzo a causa del prurito
11. Mi sono dovuto/a forzare per alzarmi dal letto
12. Ho dovuto dormire un po' durante il giorno
13. La fatica ha interferito con la mia routine quotidiana
14. Ero a pezzi
15. Ero così stanco/a che mi sono dovuto forzare a fare ciò che dovevo
16. Mi sono sentito/a così stanco da dover andare a dormire prima del solito
17. Improvvisamente mi sentivo molto affaticato/a
18. La CBP mi ha svuotato/a di ogni energia
19. Certi giorni avevo bisogno di molto tempo per fare qualsiasi cosa
20. Se un giorno ero molto indaffarato/1, avevo bisogno del giorno dopo per riprendermi
21. Ho dovuto moderare le mie attività quotidiane
22. Ho dovuto sforzarmi molto per ricordare le cose
23. Ho avuto difficoltà nel ricordare le cose da un giorno all'altro
24. La mia capacità di mantenere la concentrazione era ridotta a causa della CBP.
25. Ho avuto difficoltà a stare dietro alle conversazioni.
26. Ho trovato difficile concentrarmi su qualsiasi cosa
27. Ho avuto difficoltà nel ricordare cosa volevo fare
28. A causa della CBP le cose che ero abituato/a a fare ora mi provocano più stress
29. La mia vita sessuale ha risentito della CBP

30. Avere la CBP mi butta giù
31. Sento di trascurare la mia famiglia a causa della CBP.
32. A causa della CBP mi sento in colpa perché non posso fare ciò che era mia abitudine fare
33. Mi preoccupa come sarà la mia CBP in futuro

Per rispondere alle domande seguenti cerchi la risposta che vuole dare, come nell'esempio che segue: Per nulla; Poco; In qualche modo; Molto; Moltissimo.

34. Mi preoccupa come sarà la mia CBP in futuro
35. Tendo a tenere per me il fatto che ho la CBP
36. Non posso programmare le vacanze perché ho la CBP
37. La mia vita sociale si è praticamente azzerata
38. Ogni aspetto della mia vita è condizionato dalla CBP
39. La CBP ha ridotto la mia qualità di vita
40. Posso condurre una vita normale nonostante io abbia la CBP

## Questionario sull'affaticamento

L'elenco di affermazioni che segue descrive come l'affaticamento possa causare dei problemi nella vita delle persone. La preghiamo di leggere attentamente ogni affermazione e di fare un cerchio sul numero che esprime meglio in che misura l'affaticamento sia stato per lei un problema nelle ultime quattro settimane, compreso oggi. Faccia un cerchio intorno ad un solo numero per ciascuna domanda e risponda a tutte le domande: (0) Nessun problema; (1) Un lieve problema; (2) Un moderato problema; (3) Un grosso problema; (4) Un enorme problema. A causa dell'affaticamento:

1. Mi sento meno attento/1.
2. Mi sento più isolato/a dagli altri.
3. Devo ridurre il mio carico di lavoro e le responsabilità.
4. Sono di umore più variabile.
5. Ho difficoltà a prestare attenzione per un lungo periodo di tempo.
6. Mi sembra di non avere le idee chiare.
7. Sono meno efficiente nel lavoro (intendendo sia il lavoro in casa che fuori casa).
8. Devo contare di più sugli altri per farmi aiutare o per farmi fare delle cose.
9. Ho difficoltà a programmare delle attività con anticipo perché il mio

affaticamento potrebbe condizionarle

10. Sono più impacciato/a e scoordinato/a nei movimenti.
11. Mi sembra di dimenticare più facilmente le cose.
12. Sono più irritabile e mi arrabbio più facilmente.
13. Devo stare attento/a alla frequenza e alla durata delle mie attività fisiche.
14. Sono meno motivato/a a fare qualunque cosa richieda uno sforzo fisico.
15. Sono meno motivato/a a partecipare ad attività con gli altri.
16. La mia capacità di spostarmi/viaggiare fuori casa è limitata.
17. Ho difficoltà a sostenere uno sforzo fisico per lunghi periodi.
18. Trovo difficile prendere delle decisioni.
19. Ho pochi contatti con gli altri al di fuori della mia casa.
20. Le situazioni normali di tutti i giorni mi stressano.
21. Sono meno motivato/a a fare qualunque cosa che comporti un impegno mentale.
22. Evito le situazioni che mi stressano.
23. Sento che i miei muscoli cono molto più deboli di quanto dovrebbero.
24. Il mio malessere fisico è aumentato.
25. Ho difficoltà a gestire qualunque cosa nuova.
26. Sono meno capace di portare a termine dei compiti che richiedono un impegno mentale.
27. Mi sento incapace di rispondere alle aspettative che gli altri hanno verso di me.
28. Mi sento meno capace di provvedere al mio sostegno economico e a quello della mia famiglia.
29. La mia vita sessuale è meno attiva.
30. Pensieri quando sto facendo qualcosa a casa o al lavoro sono meno capace di portare a termine dei compiti che richiedono uno sforzo fisico.
31. Sono meno capace di portare a termine dei compiti che richiedono uno sforzo fisico.
32. Mi preoccupo di come gli altri vedono il mio aspetto fisico.
33. Le questioni emotive.
34. Mi sento più lento/a nel pensare.
35. Trovo difficile concentrarmi.
36. Ho difficoltà a partecipare in pieno alle attività di famiglia.

37. Devo limitare le mie attività fisiche.
38. Ho bisogno di periodi di riposo più frequenti e più lunghi.
39. Non sono in grado di dare alla mia famiglia il sostegno emotivo che dovrei.
40. Le piccole difficoltà mi sembrano enormi.

## EuroQoL-5D-5L

Sotto ciascun argomento, faccia una crocetta sulla casella (UNA SOLA) che descrive meglio la sua salute OGGI.

1. **Capacità di movimento**: Non ho difficoltà nel camminare; Ho lievi difficoltà nel camminare; Ho moderate difficoltà nel camminare; Ho gravi difficoltà nel camminare; Non sono in grado di camminare.
2. **Cura della persona**: Non ho difficoltà nel lavarmi o vestirmi; Ho lievi difficoltà nel lavarmi o vestirmi; Ho moderate difficoltà nel lavarmi o vestirmi; Ho gravi difficoltà nel lavarmi o vestirmi; Non sono in grado di lavarmi o vestirmi.
3. **Attività abituali** (per es. lavoro, studio, lavori domestici, attività familiari o di svago): Non ho difficoltà nello svolgimento delle attività abituali; Ho lievi difficoltà nello svolgimento delle attività abituali; Ho moderate difficoltà nello svolgimento delle attività abituali; Ho gravi difficoltà nello svolgimento delle attività abituali.
4. **Dolore o fastidio**: Non provo alcun dolore o fastidio; Provo lieve dolore o fastidio; Provo moderato dolore o fastidio; Provo grave dolore o fastidio; Provo estremo dolore o fastidio.
5. **Ansia o depressione**: Non sono ansioso/a o depresso/a; Sono lievemente ansioso/a o depresso/a; Sono moderatamente ansioso/a o depresso/a; Sono gravemente ansioso/a o depresso/a; Sono estremamente ansioso/a o depresso/a.

Vorremmo sapere quanto è buona o cattiva la sua salute OGGI. Questa è una scala numerata che va da 0 a 100. 100 rappresenta la migliore salute che può immaginare. 0 rappresenta la peggiore salute che può immaginare. Segni una X sul punto della scala per indicare com'è la sua

**Figure 5. EuroQoL scale.**

salute OGGI. Poi scriva, qui sotto il numero che ha segnato sulla scala numerata LA SUA SALUTE OGGI =_ (Figure 5).

# Statistical analysis

Changes in symptoms after OCA introduction were assessed by Wilcoxon paired rank test.

PBC-40 questionnaire was analyzed in each of its domains: general symptoms, itch, fatigue, cognitive impairment and social and emotional. Scores obtained in each domain were considered to be clinically significant when higher then 18, 8, 28, 15 and 34 points, respectively (61).

Response to treatment was assessed every six months, starting from month 6 since OCA prescription, using POISE and Paris II criteria.

Statistical testing was two-sided and was performed at the 0.05 alpha level. Statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp.).

# Results

From February 2018 to February 2021 a total of 34 subjects started OCA therapy for insufficient response to first line therapy with UDCA. Nineteen (55.8%) of them agreed to participate to the study and provided informed consent.

Most of patients, 17/19 (89%) were female and the median age at baseline was 62.0 (53.0-64.0) years, while median age at diagnosis was 44.0 (38.5-51.0) years. Complete features of the included patients are reported in Table 5.

**Table 5. Characteristics of study population.**

| **Characteristics** | **Value** |
|---|---|
| **Age at recruitment, *years*** | 62.0 (53.0-64.0) |
| **Female gende*r*** | 17 (89) |
| **Age at diagnosis, *years*** | 44.0 (38.5-51.0) |
| **AMA positivity** | 15 (78.9) |
| **PBC-specific ANA** | 11 (57.9) |
| **AIH-overlap syndrome** | 2 (10.5) |
| **Cirrhosis** | 5 (25) |
| **Child-Pugh class A** | 5 (25) |
| **Previous episode of decompensation** | 0 (0) |
| **Liver stiffness, *kPa*** | 7.0 (5.0-11.9) |
| **UDCA dose at OCA start,** mg/kg/day | 17 (13.6-18.0) |
| **Pruritus** | 12 (63.1) |
| **OCA duration, months** | 42.0 (24.0-58.0) |
| **OCA daily dose, *mg/day*** | 5.0 (5.0-10.0) |
| **Alkaline phosphatase, xULN** | 1.65 (1.50-2.22) |
| **Total bilirubin, x ULN** | 0.75 (0.48-1.22) |
| **AST, x ULN** | 1.00 (0.86-1.34) |
| **Platelets counts** | 248 (143-315) |
| **Itch presence** | 6 (31.5) |
| **Itch severity (VAS)** | 1.00 (0-7.00) |
| **Fatigue** | 9 (47) |

Notes: Continuous variables are reported as median (IQR) and categorical variables as absolute values (frequency). Presence of fatigue and itch was assessed as domains score >4 and >12, respectively.

Abbreviations: AMA, anti-mitochondrial antibodies, ANA, anti-nuclear antibodies, UDCA ursodeoxycholic acid, OCA, obeticholic acid.

AMA positivity was observed in 15/19 patients, while PBC-specific ANA (anti-gp210 or anti-sp100) were detected in 11/19 at the time of diagnosis. Two patients presented with AIH overlap syndrome.

Five patients were cirrhotic, all in Child-Pugh class A when starting OCA treatment. Transient elastography at the time of enrolment was available in 16 patients, with median value of 7.0 (5.0-11.9) kPa; only 1 patient exceed the cut-off for cirrhosis, showing a liver stiffness of 32.2 kPa.

Total bilirubin at the beginning of OCA therapy was normal in 11/17 patients, with a median value of 0.75 (0.48-1.22) x ULN.

All patients were under UDCA treatment at the time of starting OCA, with a median dose of 17 (13.6-18.0) mg/kg/die.

History of pruritus was present in 11/17. Nine of them were taking antipruritic drugs when starting OCA: 3 took fibrates and 6 took other drugs (*i.e.*, anti-histaminic, cholestyramine or sertraline).

In order to minimize the risk of new onset/aggravation of pruritus, patients were instructed to start OCA treatment at the dosage of 5 mg every other day for the first 2 weeks and then increase to 5 mg/day if well tolerated.

At the time of data lock the median duration of OCA treatment was 42.0 (24.0-58.0) months, while median OCA dose was 5.0 (5.0-10.0) mg/die; 9 (47.4%) patients were taking 10 mg/die, 9 (47.4%) patients taking 5 mg/die and 1 (5.3%) patient was given 5 mg every three days due to presence of cirrhosis with signs of portal hypertension.

# Changes in biochemistry after OCA start

A progressive reduction of ALP was observed and resulted significant compared to baseline values at 12, 36 and 48 months from starting OCA (Figure 6).

ALP reduction < 1.5xULN and, in a lesser extent, normalization was achieved in a considerable portion of patients at different time points (Figure 7)

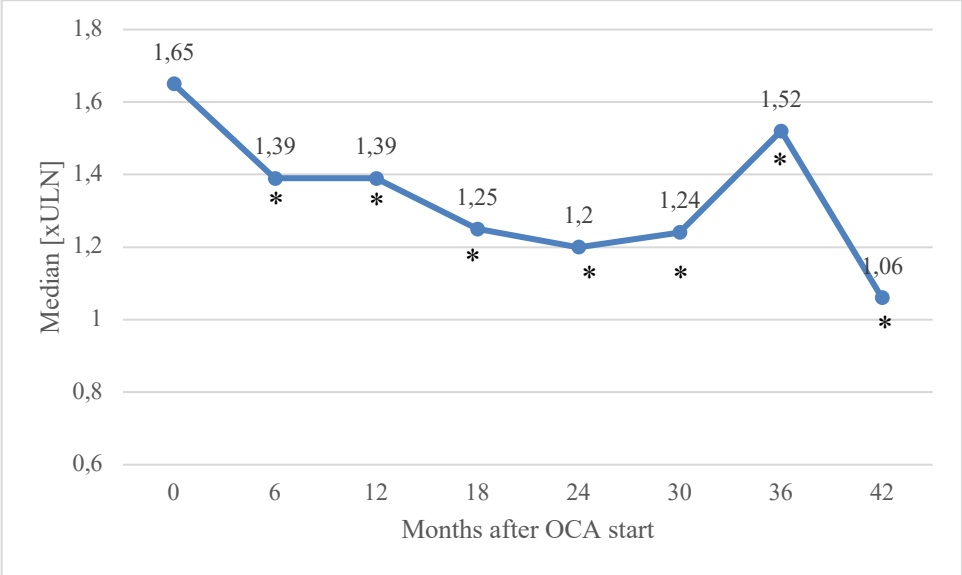



**Figure 6. ALP changes after OCA introduction. *=Significant results (p<0.05) in paired t tests month 0 vs. month n.**

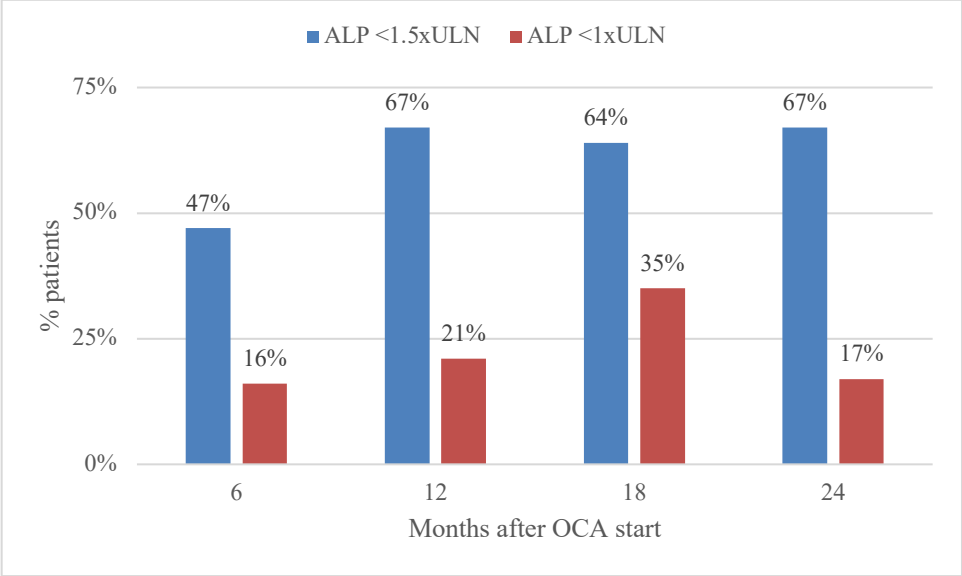



**Figure 7. Rates of matching of reduction < 1.5xULN and normalization of ALP from 6 to 24 months of treatment**

ALP levels in patients with cirrhosis were lower compared to non-cirrhotic, even not significantly, in the first 24 months after OCA introduction and then tend to increase (Figure 8).

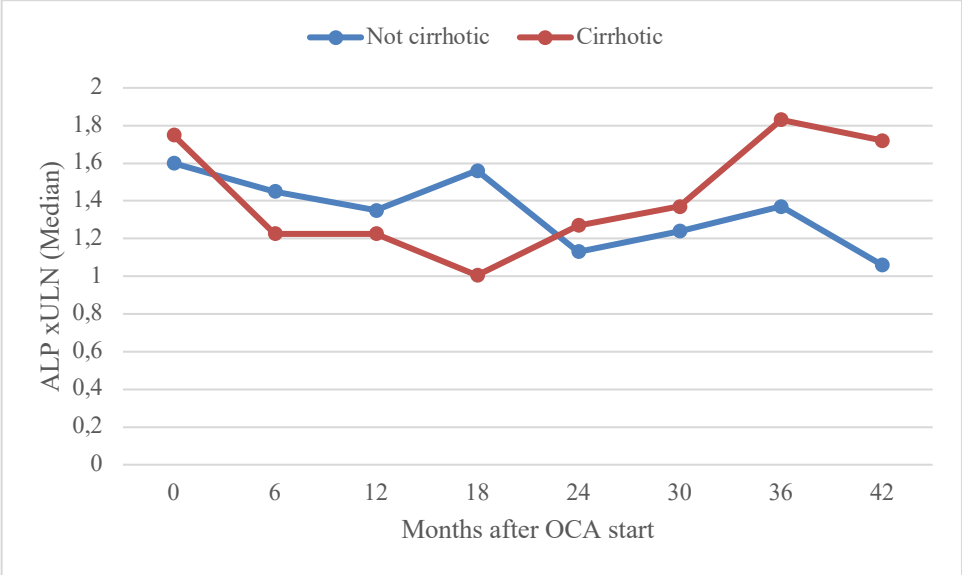



**Figure 8. ALP xULN (median) modifications from baseline to 48 months of treatment in cirrhotic (red) and non-cirrhotic (blue) patients.**

A significant reduction of gGT values was also shown at every evaluation compared to baseline (Figure 9).

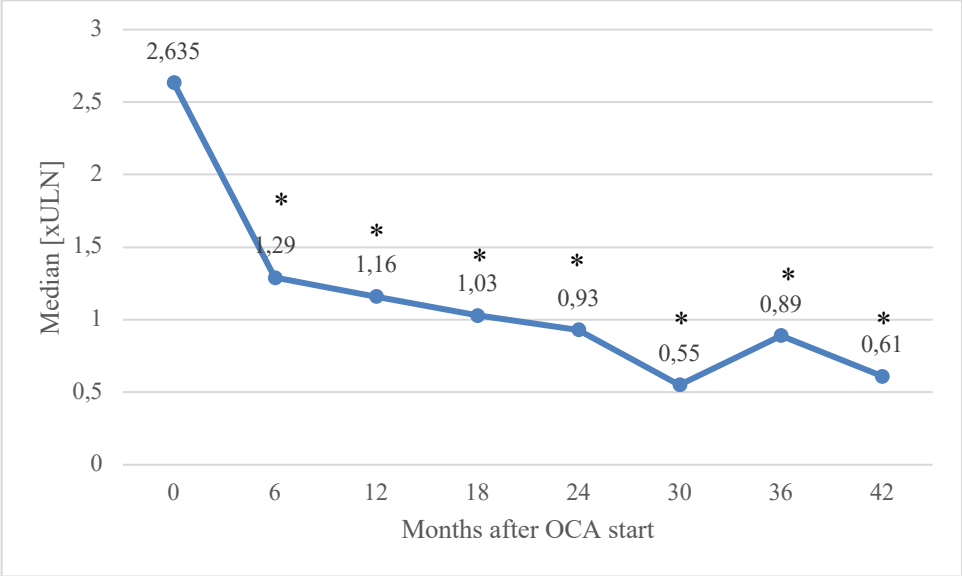



**Figure 9. GGT changes after OCA introduction. * = Significant results in paired t tests month 0 vs. month n.**

Compared to baseline value, significant reduction of AST was shown at 6, 12, 18, 24, 30, 42 and 48 months and of ALT at each time points considered (Figure 10).

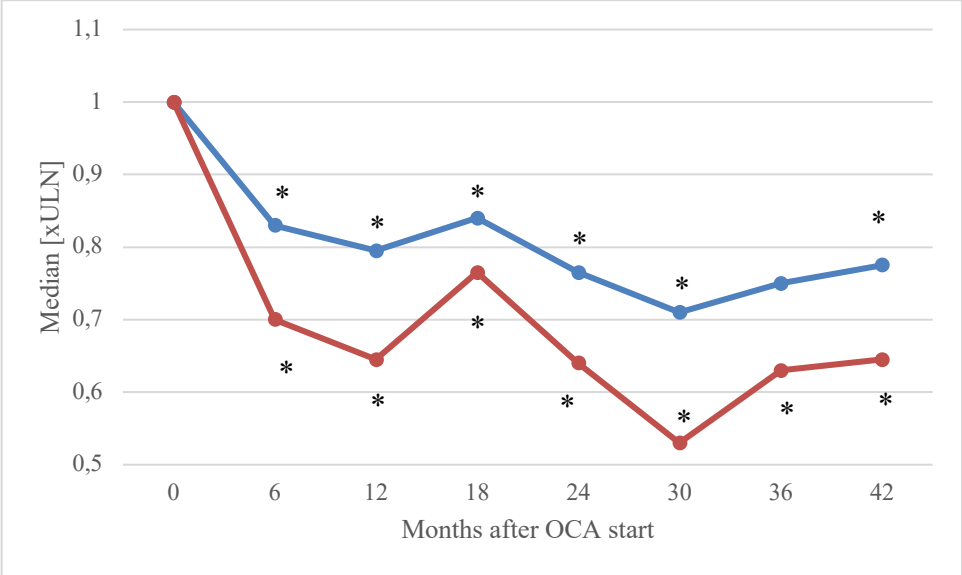



**Figure 10. AST (blue) and ALT (red) modification after OCA introduction. * = Significant results in paired t tests month 0 vs. month n.**

A significant reduction from baseline of total bilirubin was observed from 6 to 24 months after OCA introduction (Figure 11).

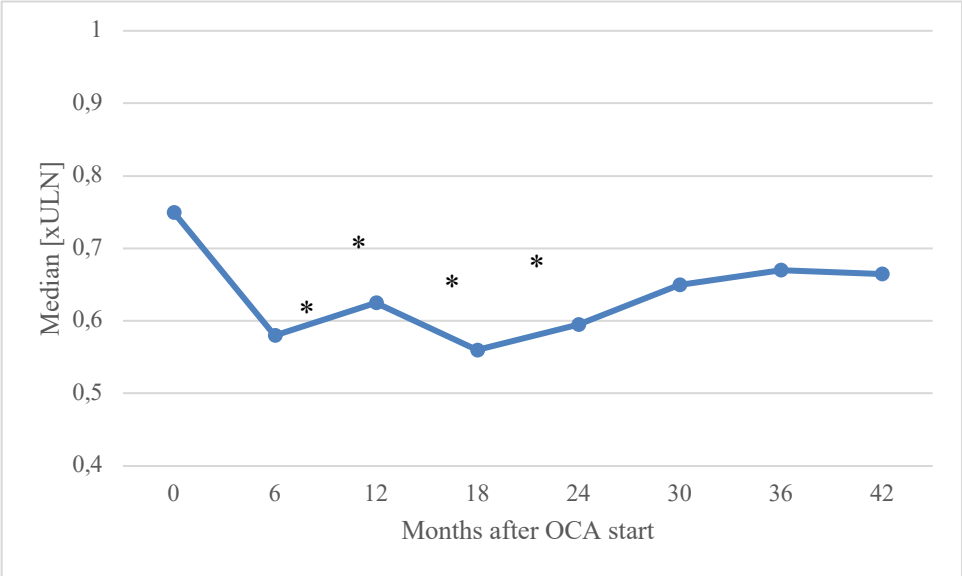



**Figure 11. Total bilirubin modifications after OCA introduction. (*) = Significant results in paired t tests month 0 vs. month n.**

No changes of INR when comparing baseline level were observed after OCA introduction (data not shown).

No significant changes from baseline in albumin circulating levels were observed (data not shown).

Changes in the number of platelets were various, inconstant and not statistically significant from 6 to 42 months of treatment (Figure 12).

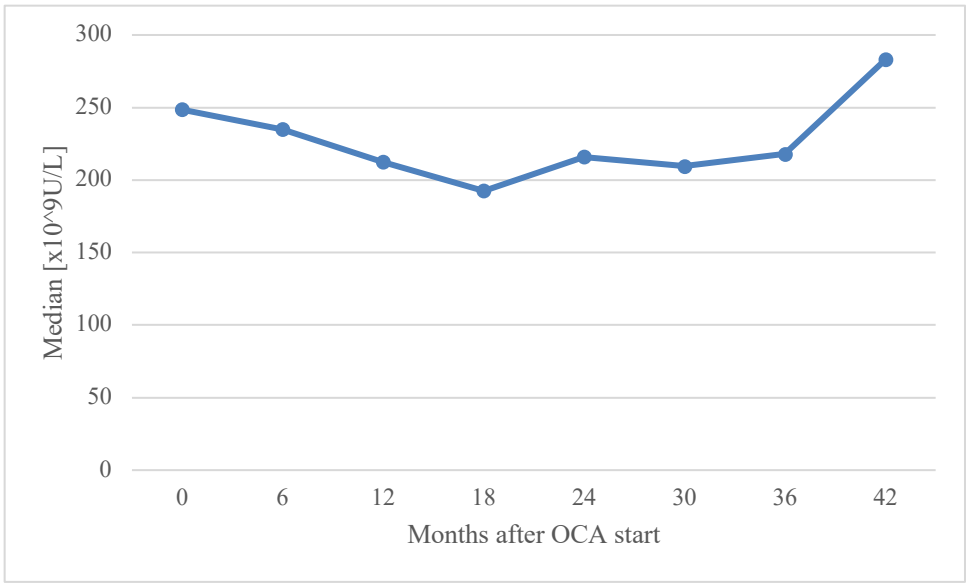



**Figure 12. Platelets changes after OCA introduction.**

Changes in total cholesterol were various, a significant reduction was observed after 18 months of treatment (201 (176.5-227) vs. 172.5 (147-212)). Modifications in HDL were inconstant, significant reductions were observed after 18, 24 and 36 months of therapy with OCA (Figure 13).

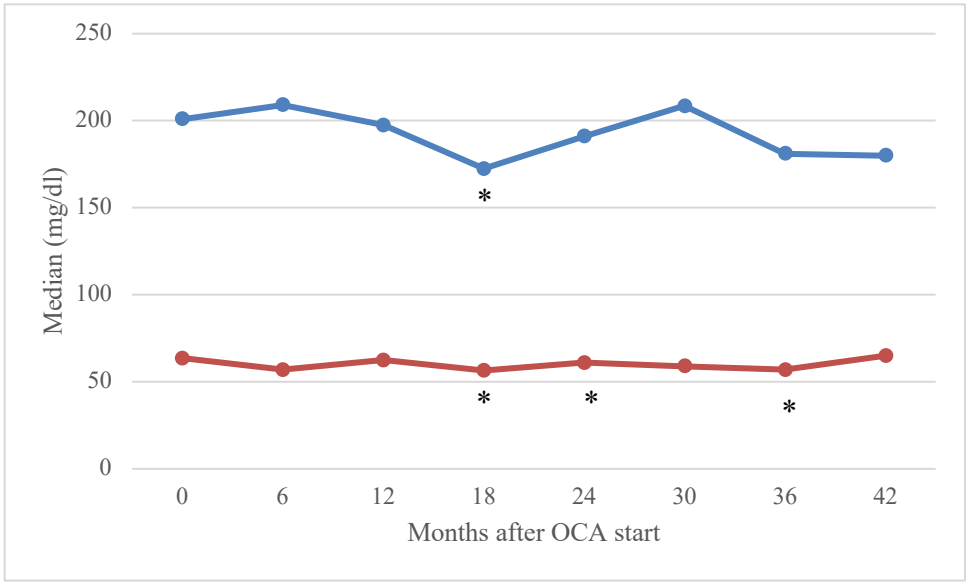



**Figure 13. Total cholesterol (blue) and HDL (red) changes after OCA introduction. * = Significant results in paired t tests month 0 vs. month n.**

# Liver stiffness changes after OCA start

A reduction, despite non-significant, of liver stiffness from baseline to each year of observation was observed (Figure 14).

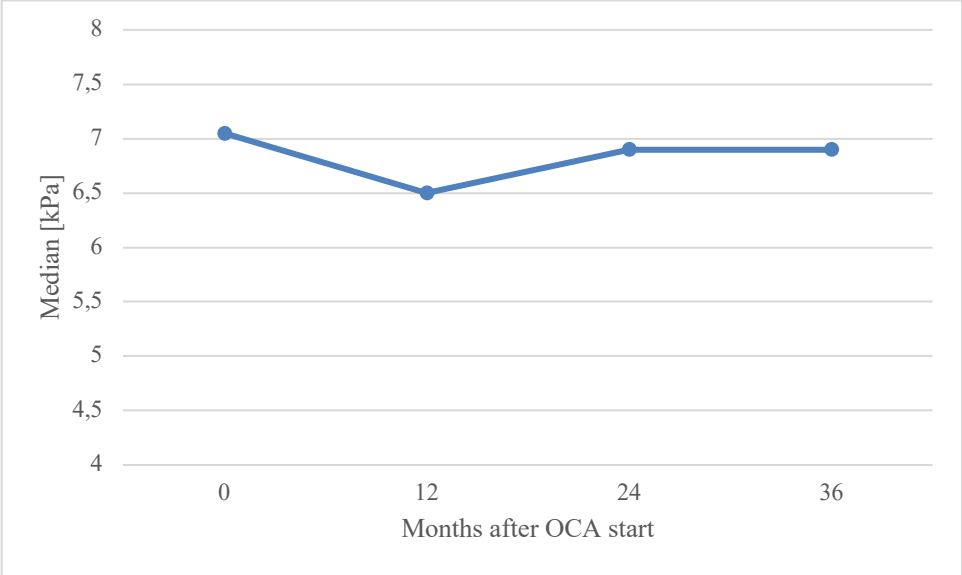



**Figure 14. Liver stiffness (assessed with FibroScan) changes after OCA introduction.**

# Assessment of response to therapy

## POISE criteria

POISE criteria[1], when available, was used to assess response to OCA treatment every 6 months for 24 months.

- After 6 months of treatment 5/13 patients (38.5%) met POISE criteria.
- After 12 months of treatment 5/15 patients (33.3%).
- After 18 months of treatment 4/12 patients (33.3%).
- After 24 months of treatment 6/12 patients (50.0%).

## Paris II criteria

Paris II[2] criteria was also employed to evaluate response to treatment with OCA at the same time points used for the previous ones (Figure 15).

- After 6 months: 4/14 (28.6%) patients met Paris II criteria.

[1]ALP $\leq$1.67xULN + $\Delta$ALP $\geq$15% + TB $\leq$1xULN

[2]ALP $\leq$1.5xULN + AST <1.5xULN + TB<1mg/dl

- After 12 months: 5/15 (33.3%) patients met Paris II criteria.
- After 18 months: 5/15 (33.3%) patients met Paris II criteria.
- After 24 months: 5/13 (38.5%) patients met Paris II criteria.

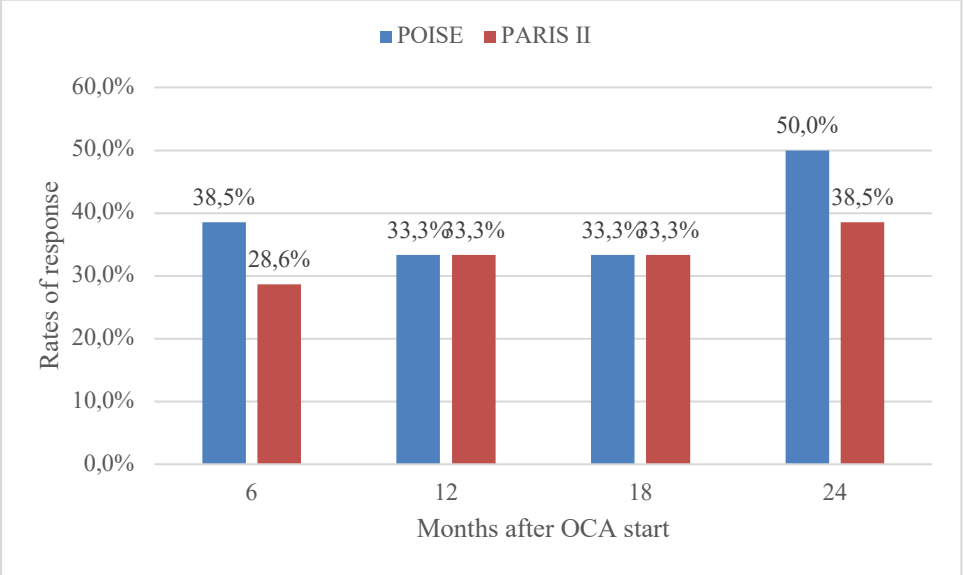



**Figure 15. Response to therapy: rates of matching of POISE and Paris II criteria.**

# Symptoms and quality of life after OCA start

Treatment with obeticholic acid was generally well tolerated, with no discontinuation due to adverse events (AEs). All patients reported an improvement in general wellbeing after OCA introduction at each timepoints. Two patients over 19 reported the new onset of pruritus, accompanied by fatigue and insomnia after OCA introduction, however they did not need specific treatment of pruritus since it was of mild grade.

Nineteen patients joined the study and completed at least one year of treatment at the time of data lock, handing over specific questionnaires (median 5; IQR 2.5-6-.75 questionnaires/patient).

PBC-40 questionnaire was analysed in all its domains, every six months, for two years. There were no statistically significant changes in any domain of the questionnaire. However, we observed non-significant improvements in the following domains (Figure 16 and 17):

- **General symptoms** at 6, 12 and 24 months of treatment: 16 (11-19) *vs.* 15(10-19) (p=0.779), 16.0 (11.0-19.0) *vs.* 15 (11-21) (p=0.719), 16(11-19) *vs.* 14(12-15) (p=0.481).
- **Fatigue domain** at 6, 12 and 24 months of treatment: 27(12-32) *vs.* 20(11-34) (p=0.440); 27(12-32) *vs.* 11 (11-31) (p=0.726); 27 (12.-32) *vs.* 21 (11-31) (p=0.916), respectively.
- **Itch domain** at 12 and 24 months: 3 (0-6) *vs.* 3 (2-6) (p=0.796); 3 (0-6) *vs.* 3 (0-4) (p=0.396).
- **Cognitive impairment** at 12 months: 9 (6-15) *vs.* 7 (6-11) (p=0.152).
- **Emotional impairment** at 24 months: 8 (5-10) *vs.* 6 (5-8) (p=0.798).
- **Social impairment** at 6 months: 30(27-32) *vs.* 30 (27-33) (p=0.766).

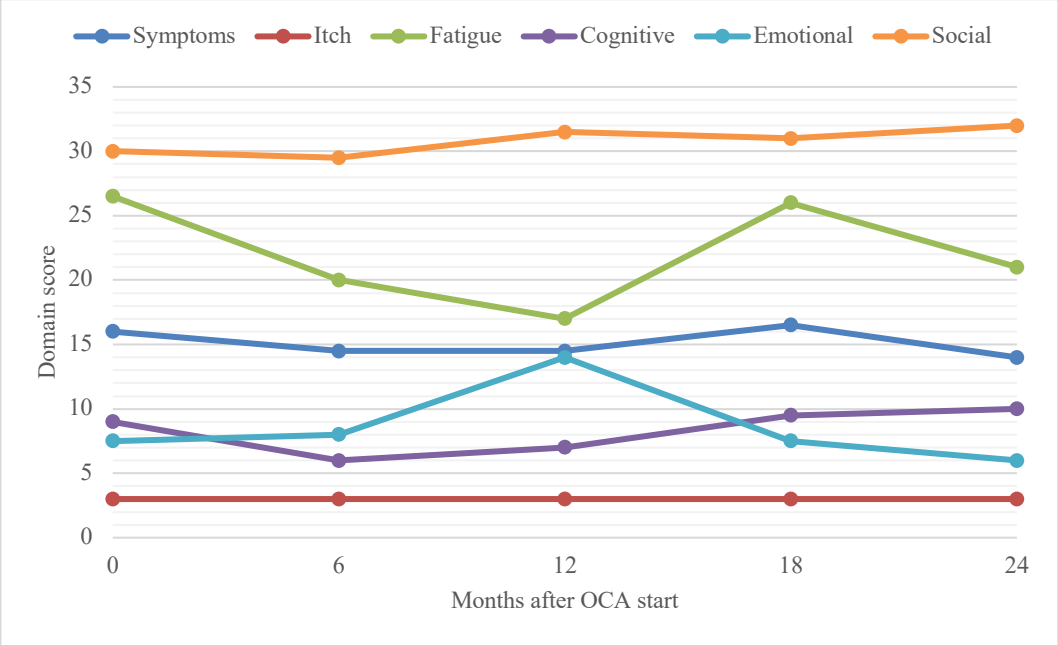



**Figure 16. Changes in PBC-40 questionnaire domains over time from baseline to 24 months.**

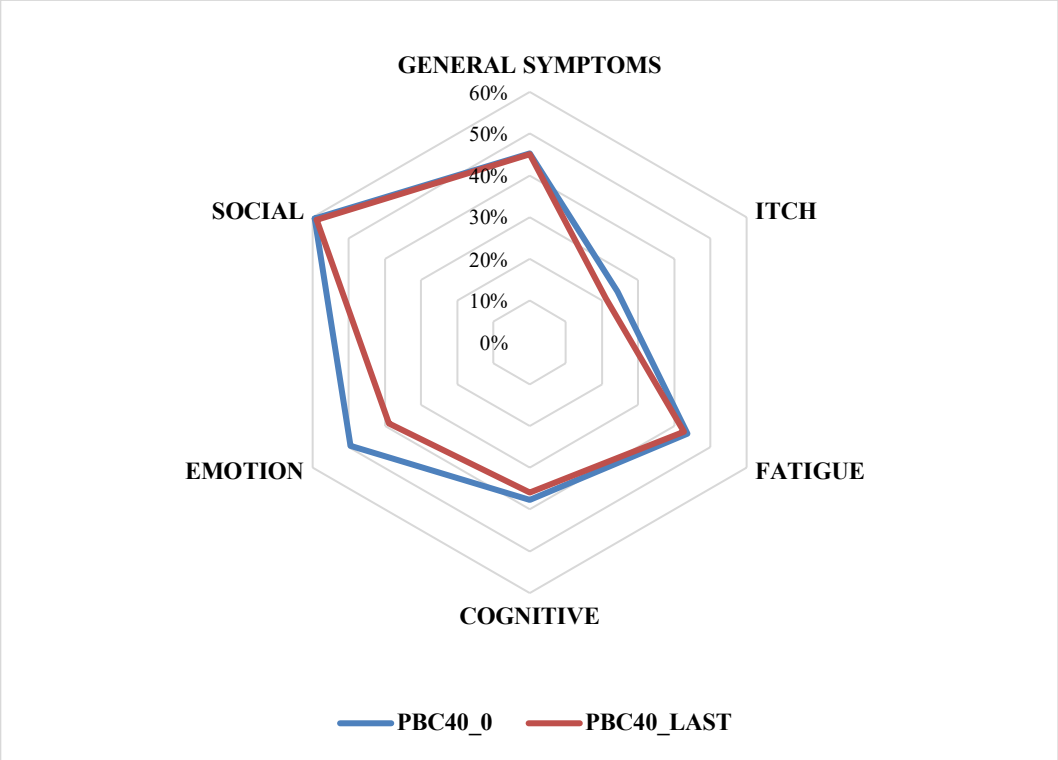
## Clinical significance of symptoms

We analysed the frequency of clinically significant symptoms, according to the cited definition, at baseline and at last evaluation available after OCA introduction and we failed to observe any significant modifications (Table 6) (61).

**Table 6. Evaluation of clinically significant symptoms before and after OCA treatment**

| PBC-40 domain (no. items) | Clinical significance | Pre-OCA n(%) | Last evaluation n (%) | p |
|---|---|---|---|---|
| *Fatigue* | ≥ 29 | 5 (26) | 5 (26) | 0.480 |
| *Cognitive impairment (6)* | ≥16 | 2 (10) | 3 (16) | 1.000 |
| *Itch (3)* | ≥9 | 1 (5) | 1 (5) | 1.000 |
| *Social (10)* | ≥29 | 10 (52) | 11 (58) | 0.617 |
| *Emotional (3)* | ≥8 | 7 (37) | 4 (21) | 0.375 |
| *General symptoms (7)* | ≥11 | 4 (21) | 6 (32) | 1.000 |

**Figure 17. Variation between baseline (blue) and last (red) evaluation of PBC-40 questionnaire domains (% total domain scores).**



## 5-D Itch Scale

A slight, even if not significant, improvement in 5-D Itch Scale was observed after 12, 36 and 48 months of therapy with OCA: 3.0(0-8.5) *vs.* 2(0-7.0) (p=0.731), 3.0(0-8.5) *vs.* 0.5(0-2.5) (p=0.197), 3.0(0-8.5) *vs.* 1.0(0-3.5) (p=0.180), respectively.

## Visual Analogue Scale (VAS)

A non-significant reduction in VAS of pruritus was observed after 36 months of treatment, while no changes were assessed at 24 and 48 months (Figure 18).

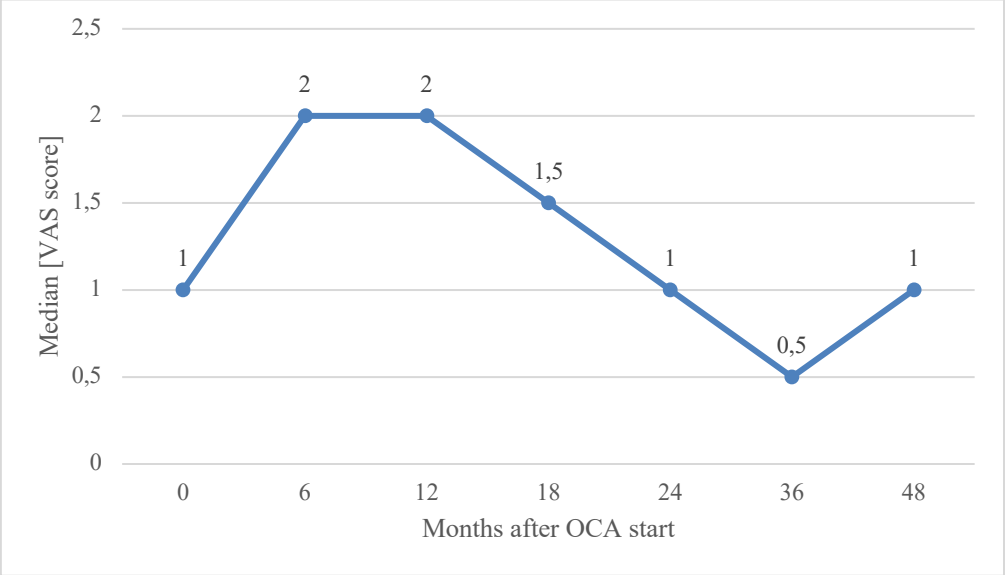



**Figure 18. VAS of pruritus over time of evaluation.**

## Fatigue Impact Scale (FIS)

Remarkable improvements were assessed in FIS, although not statistically significant. Comparing to baseline FIS score showed a reduction after 36-months of OCA treatment, which was close to statistical significance: 45 (0-82) vs. 10.5 (0-42) (p=0.066) (Figure 19).

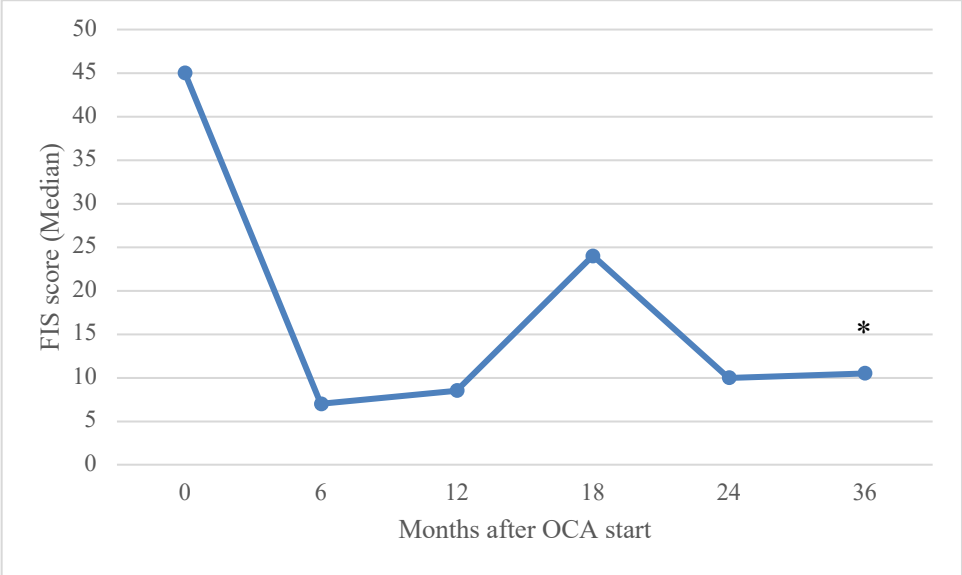



**Figure 19. Fatigue Impact Scale (FIS) evaluation from baseline to 48 months of treatment. (*): p=0.066**

# EuroQoL 5D-5L (EQ-5D-5L)

A substantial stability in EQ-5D-5L were seen during OCA treatment with median ranges varying from 79.5 to 86 (p=n.s.) (Figure 20).

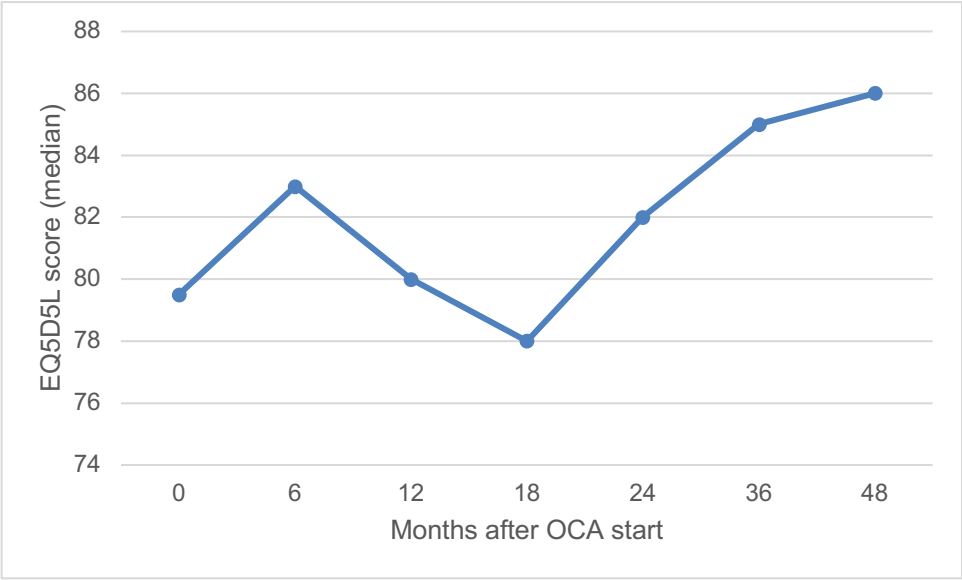



**Figure 20. EQ5D-5L questionnaire results at given timepoints.**

# Discussion

In this phase 4 observational study, obeticholic acid (OCA) was administered in combination with UDCA, in those patients who had insufficient response to first line treatment, as per AIFA indications and the response in terms of biochemistry changes, liver stiffness changes, symptoms and quality of life was assessed every 6 months. Nineteen patients were included with a median duration of OCA treatment of 42 months and we observe a biochemical response as per POISE endpoint in 50% and 52% of patients, after 24 and 42 months of treatment, respectively. All patients reported an improvement of general wellbeing after OCA introduction, moreover a trend toward a significant reduction of fatigue after 36 months was observed. Finally, a stability of different PBC symptoms domains with no aggravation of pruritus leading to treatment discontinuation or reduction was observed.

Compared to the POISE cohort, the patients included in this study were older at the time of starting OCA (62 *vs.* 56 y.), with 4 years longer disease duration. The proportion of female gender was comparable (89% *vs.* 93%). Two patients with AIH-overlap syndromes were also included, unlike POISE trial. In our cohort the totality of patients was treated with UDCA at the time of starting OCA, with a median dose of 17 (13.6-18.0) mg/kg/die, while in the phase III trial only 93% of patients were treated with UDCA, at a similar dose, which represent the highest recommended.

In our study, differently from the POISE trial, we decided to start OCA on 5 mg every other day in the first 2 weeks in order to possibly minimize the burden of symptoms, mainly pruritus, that could have led to early treatment discontinuation. After 2 weeks from starting OCA, if well tolerated, the dosage was increased at 5 mg/day in all patients and then, at 6 months, increased at 10 mg/day if complete response was not achieved. By adopting this scheme of gradual titration in the first 2 weeks, the treatment was very well tolerated, and no patients discontinued the drug for appearance or aggravation of pruritus or other symptoms. At the time of data lock, 9 (47.4%) patients reached the maximum dosage.

Improvements in liver biochemistry were documented since the first follow-up visit

(6 months), showing a rapid, significant[3] and persistent enhancement in serum markers of cholestasis (ALP and GGT) and hepatocellular enzymes (AST and ALT). Furthermore, normalization of ALP was observed in 16%, 21%, 35% and 17% of patients at 6, 12, 18 and 24 months respectively. This highlights that there is still space for improvement the treatment of patients with PBC since ALP normalization has been clearly associated with improved prognosis (126).

Significant changes in total bilirubin were assessed after 12, 18 and 24 months of treatment. Changes in platelets count were assessed at every time point, with a persistent and non-clinically, nor statistically significant reduction between 12 and 30 months of treatment.

On the other hand, changes in liver stiffness assessed FibroScan were inconstant, with an initial reduction after 12 months of treatment, followed by an increase compared to baseline and a subsequent reduction at 36 months, thus indicating a substantial stability over time of LS. In our study LS, was lower than in the POISE cohort, at the time of enrolment and after 12 months of treatment (7.05 vs. 10.70 and 6.5 vs. 10.06, respectively), and of that observed in the Canadian cohort (7.05 vs. 10.70). The Iberian real-world study did not use FibroScan in order to assess LS, surrogate markers as FIB-4 were adopted, which did not significantly change throughout the period of observation; similar to what was observed in our cohort.

An increasing percentage of subject, throughout the observation period, achieved POISE and Paris-II criteria of response. These data are lower when compared to POISE trial, in which almost 50% of patients reached the composite primary endpoint at 12 months, while in our cohort we observed that only 33% of patients reached the endpoint at 12 months but 50% at 24 months. Many hypotheses could explain these data:

1. Our population has a longer story of non-response to UDCA.
2. Almost 50% of patients were younger than 50 years old at the time of diagnosis, factor that is associated with a poorer prognosis.
3. A higher proportion of patients were cirrhotic at the time of the enrolment (25% vs. 20%).

There were not significant changes in HrQoL of PBC people treated with OCA, nor

[3] $p < 0.05$

improvements neither worsening. Nevertheless, pruritus, that is a major concern in PBC patients, as it represents one of the most affecting symptoms and, at the same time, a common side effect of OCA, was thoroughly investigated. In our cohort, nor PBC-40 specific section neither 5-D Itch Scale or VAS showed worsening of pruritus after starting OCA treatment and no one discontinued the drug due to side effects, differently from the POISE trial where 10% of patients discontinued treatment to worsening or new onset of pruritus. In addition to that, no one needed to start antipruritic drug after OCA introduction. Before starting OCA, 5 (26%) patients were treated for pruritus with cholestyramine (2 patients), fibrates (1 patient), anti-histaminic (1 patient) and sertraline (1 patient). During treatment with OCA, 1 patient, previously treated with cholestyramine changed to anti-histaminic and then fenofibrate. Interestingly, those treated with fibrates, when compared to other antipruritic drugs, had higher intensity of pruritus throughout the observation period, as observed in the PBC-40 Itch domain.

We believe that one of the possible reasons for the low frequency of pruritus aggravation or new-onset that we observed in our cohort is related to the scheme adopted in the first 2 weeks of treatment, during which we administer 5 mg every other day. Indeed, PK studies have documented that steady-state systemic exposure ($AUC_{0\text{-}24h}$) is achieved on Day 14 of total obeticholic acid and is 4.2- fold the systemic exposure ($AUC_{0\text{-}24h}$) achieved on Day 1 after 5 mg once daily dosing. Such a high systemic exposure might be responsible for the onset or worsening of pruritus. It has to be considered, in fact, that FXR plays a pivotal role both in the pharmacodynamic of OCA and in the onset of pruritus (46). Thus, we might hypothesize that in our cohort the steady-state systemic exposure is reached more slowly and this may prevent the occurrence of severe pruritus in these patients. However, further studies are needed to clarify this point.

Fatigue, the most common symptom in PBC, was widely reported by our patients both at the enrolment and at the last evaluation. Clinically significant fatigue, defined as moderate or severe (61), was reported by 5 patients, both at the enrolment and at last follow-up visit. Encouraging results came from Fatigue Impact Scale (FIS) that showed improvements, close to statistical significance at 36 months of treatment. We might speculate on the possible effects of OCA on central component of fatigue in PBC patients. Gee *et al.* documented the role played by FXR in cerebral microcirculation and in enhancing short term memory in bile

duct-ligated mice, a well-established rodent model of cholestasis (127). A similar effect could be hypothesized in PBC patients and this may impact on fatigue. However, in our cohort we did not observe an improvement in cognitive domain of the PBC-40 but, otherwise, a non-significant improvement in the emotional domain was observed. Further investigations would be needed in order to establish a link between these two aspects.

When analyzing clinical manifestations of PBC other than pruritus and fatigue, we found substantial stability of clinically significant symptoms over OCA treatment. However, we observed a non-significant reduction in the emotional impairment domain, thus meaning an improvement in the emotional domain, that is concordant with the general wellbeing reported by patients after OCA introduction. This is probably due to an enhancement in treatment confidence caused by the introduction of an add-on therapy, that is both effective in ameliorating liver tests and very well tolerated by patients. (124). Relationship between, patients' trust in health-care professionals and therapy adherence has been investigated, especially in primary medical care setting (128) and, in the last years, also in chronic liver disease field (123). These studies show that treatment confidence plays a critical role in effectiveness of treatment, in fact they reported that overly optimistic expectations can have a positive impact on response to therapy, thanks to the activation of self-healing mechanisms or producing a placebo response (129).

This is the first real world prospective study on the use of OCA in a well characterized cohort of PBC patients who started add-on 2$^{nd}$ line therapy with OCA according to strict criteria provided by the Italian Medicine Agency that evaluate not only response as assessed by biochemistry but even health-related quality of life in this class of patients. Moreover, median duration of OCA therapy was 42 months that is a long time of observation and providing long-term safety data.

The limitations of the study are the restricted number of subjects included, that may have limited the statistical significance and the number of missing data in some timepoints due to the lack of external monitoring during the study's conduction.

In conclusion, in this 5-years phase 4 observational trial it has been possible to assess that people with PBC and insufficient response to UDCA experienced biochemical and subjective improvement after OCA introduction and no significant aggravation of objectively assessed PBC symptoms and HRQoL thus indicating that this treatment is effective and safe and seems to positively affect treatment

confidence in PBC patients.

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