REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
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DOI: 10.17235/reed.2018.5662/2018
Link: PubMed (Epub ahead of print)

Please cite this article as:
Martínez Javier, Aguilera Lara, Albillos Agustín. Risk stratification and treatment of primary biliary cholangitis. Rev Esp Enferm Dig 2018. doi: 10.17235/reed.2018.5662/2018.

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Risk stratification and treatment of primary biliary cholangitis

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Received: 25/04/2018

Accepted: 11/09/2018

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ABSTRACT

Primary biliary cholangitis is a chronic liver disorder characterized by progressive cholestasis that may evolve to liver cirrhosis. While ursodeoxycholic acid is the treatment of choice, around 30% of patients do not respond to this therapy. These patients have a poorer prognosis, hence should be identified early in order to be offered therapy options. Along these lines, improved understanding of the condition's pathophysiology has allowed the development of newer drugs, including obeticholic acid and fibrates. This review offers a perspective on risk stratification and treatment for these patients, from ursodeoxycholic acid to second-line treatments.

Key words: Cirrhosis. Ursodeoxycholic acid. Obeticholic acid. Fibrates. Budesonide.

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INTRODUCTION

Primary biliary cholangitis (PBC) is an autoimmune, progressive disease of the liver of unknown origin. It is characterized by inflammation and destruction of intrahepatic bile ducts, which results in progressive cholestasis that may potentially lead to liver cirrhosis.

It primarily affects middle-aged women (from 40 to 60 years of age). In recent decades a change in epidemiology has been noticed, and older women with milder presentations are now diagnosed with the condition (1-3).

Diagnosis is suspected from increased alkaline phosphatase and/or bilirubin levels, and established by antimitochondrial antibodies (AMA), which are found in 90-95% of cases. Although included among diagnostic criteria, diagnosis confirmation with liver biopsy is now exceptional, and restricted to cases with doubtful diagnosis or suspected overlap syndrome (2-4).

PBC treatment with ursodeoxycholic acid (UDCA) represented a paradigm shift as it changes the condition's natural histoy by improving liver chemistry and survival (2). Hence, the number of patients on the waitlist for liver transplantation was reduced by half over the past 20 years in the United Kingdom and the United States (5). However, 30% of patients do not respond to UDCA, implying a poorer prognosis and high risk for disease progression. Early patient identification would allow the use of second-line treatments to improve prognosis.

RISK STRATIFICATION

The course of PBC is variable – some patients have slowly progressive disease whereas others develop advanced fibrosis and liver cirrhosis within few years. This varying risk of progression must be assessed in each individual patient to estimate their prognosis. To this end various demographic (age and gender), clinical (symptoms), laboratory, and serological parameters are evaluated, as well as disease stage based on fibrosis extent and response to treatment (6) (Table 1).

Demographic factors

Age and sex are both factors with an impact on response to treatment, and play therefore a role in prognosis. As a general rule, patients diagnosed before 45 years of age and males have poorer responses to therapy (6,7). The association of age, sex, and response to treatment is inconsistent between males and females (Fig. 1). The role of age is much stronger in women, and response to treatment is worse in younger women as compared to women older than 50 years. This is likely due clinical overlap forms with autoimmune hepatitis, more common at an earlier age. As may be seen in figure 1, the impact of age on response to treatment is also apparent in males, but less markedly so (1).

In males PBC is diagnosed in later, more advanced stages, as changes in liver chemistry are usually attributed to causes other than this disease. These factors, together with poorer response to therapy and higher risk for hepatocellular carcinoma, render PBC prognosis worse in males versus females (7,8).

Clinical manifestations

In all, 50% of patients with PBC have pruritus or fatigue over the course of disease, and both symptoms are associated with impaired quality of life (9).

Some recent studies find an association of symptoms with poorer response tom treatment and poorer prognosis (10,11). However, there is much controversy about the actual impact of symptoms on prognosis, and there is no evidence that symptoms may add discriminating value over risk stratification factors (12).

Lab parameters

Alkaline phosphatase (AP) is also related to PBC prognosis (13,14). Its great advantage over other labs is that it increases early in the course of disease, when no symptoms have yet developed and liver involvement remains mild. Therefore, AP is the most valuable and useful lab parameter in clinical practice, as it allows the disease to be diagnosed during early stages (6). Another advantage of AP is the fact that it allows to monitor treatment response, as response indices include multiple AP cut-offs with high prognostic value (13).

Bilirubin and albumin are also related to PBC prognosis. Both allow to discriminate progression risk, and attention must be paid to minimal bilirubin changes as even values slightly above 1 mg/dL, still within normal range, have been seen to be associated with poorer prognosis (14). Progression risk is low when both markers are normal, and rises when one or specially the two of them show abnormal levels (13,14). The drawback of bilirubin and albumin as progression risk factors, as opposed to AP, is that changes occur in advanced stages, hence they represent poor markers for risk stratification in patients diagnosed during early stages.

Serologic profile

Some studies have associated the presence of antinuclear antibodies gp-210 and sp-100 with more severe forms of the disease, and the presence of anticentromere antibodies with the presence of portal hypertension (15,16). However, no studies have prospectively validated the predictive value of said antibodies, and their clinical usefulness is therefore scarce (12).

Disease stage

Liver fibrosis is the histology parameter that best correlates with disease stage, and also a prognostic determinant; indeed, patients with mild fibrosis at diagnosis have a much higher survival rate at 5 years when compared to those with advanced fibrosis (96% *vs* 60%) (17).

Non-invasive methods have been developed to assess fibrosis. Transient elastography (Fibroscan®) is the most commonly used approach. This technique allows to stratify progression risk both statically and dynamically. The study by Corpechot et al found that levels above 9.6 kPa at diagnosis were associated with poorer prognosis, a higher risk of hepatic decompensation, and greater mortality (18). Furthermore, dynamic liver stiffness assessment has also been seen to have prognostic implications in that patients with a yearly increase above 2.1 kPa are at higher risk for complications (18).

In addition to fibrosis other histological parameters exist, including inflammatory infiltration and bile duct destruction, that are correlated with disease stage. However, since histology is not required for the diagnosis of PBC, and liver fibrosis assessment

with noninvasive methods has been significantly advanced, liver biopsy is no longer relevant in assessing disease stage. In spite of this, biopsy taking is advisable for patients where an association with autoimmune hepatitis is suspected (overlap syndrome), and should be considered for those who respond inadequately to treatment (12).

Response to treatment

Response to treatment is the most important prognostic factor for patients with PBC (19). Patients who fail to respond to treatment are at higher risk for progression of their liver condition, and at higher risk for hepatocellular carcinoma and poorer survival (20). In contrast, responders have a much better prognosis with survival rates similar to those of the healthy population (6,21-23).

Response to treatment is assessed based on the changes experienced by biochemical markers such bilirubin and alkaline phosphatase, which represent validated predictive factors in the setting of PBC (14). In fact, bilirubin and alkaline phosphatase are part of the multiple treatment response indices that have been developed (Table 2).

All these indices have proven useful, are easy to calculate, and exhibit high specificity. The assessment of treatment response with these indices must take place at 6-12 months following therapy onset, and assessment at 6 months seems just as useful as at 12 months (31). Paris I criteria were most widely used. However, a combination of this index with the AST-to-platelets ratio index (APRI) was seen to improve risk stratification (6). Therefore, the index was updated and became a Paris II criterion, its use becoming widespread because of its highest discrimination power and improved usefulness in early disease stages (27).

Despite their indisputable utility, all these criteria fail to include other predictive variables such as disease stage (discussed above), and provide a dichotomous result (responder/non- responder), hence they allow no dynamic risk assessment and are unfit to classify patients with intermediate risk only meeting some of the response criteria in each index. In the last few years, based on collaborative studies that managed to enroll a high number of subjects, additional prognostic indices have been developed (UK-PBC Risk Score and GLOBE index) (8,32,33). The main advantage of

these newer indices is that their results may be interpreted in an ongoing, dynamic manner, which permits an improved correlation between risk and time, as well as an improved stratification of patients at intermediate risk.

Their calculations are complex as they include logarithmic formulas, but calculators are available on the World Wide Web, which simplifies their use in clinical practice (https://www.globalpbc.com/globe, https://www.uk-pbc.com/resources/tools/riskcalculator).

TREATMENT OF PRIMARY BILIARY CHOLANGITIS

First-line therapy: ursodeoxycholic acid (UDCA)

UDCA is a hydrophilic bile acid that is primarily absorbed in the small bowel and via the portal system reaches hepatocytes, where it is conjugated to be excreted in the bile. At therapeutic doses UDCA modifies the bile composition and becomes its primary bile acid (40-60%), thus reducing the levels of endogenous bile acids, which are more cytotoxic. Based on experimental studies other supplementary mechanisms of action have been posited – it stimulates bile acid secretion, neutralizes intracellular cytotoxic elements, and has immunomodulating, antiapoptotic and antioxidant properties (34,35).

UDCA is the treatment of choice for PBC, and must be maintained indefinitely either as monotherapy or combined with current second-line therapies. It must be dosed at 13-15 mg/kg/day, preferably in two doses to be taken with food. While the drug is usually safe, gradually increasing doses every 2-3 days precludes diarrhea and pruritus. Dose adjustment to renal or liver function is unnecessary (36).

In all, 60-70% of patients respond to UDCA, which is associated with improved liver chemistry and histology, reduced progression to cirrhosis, and improved survival, particularly when administered early in the course of disease (21-23,36-38). Female gender, advanced age at therapy onset, and early disease stage are independently associated with better response to UDCA (6).

Around 30% of patients do not respond to UDCA, this being a major predictor of poor prognosis that is associated with disease progression and decreased survival (20,22). In this patients doubling UDCA doses is not indicated, and second-line therapies should

be considered (39). Male gender and advanced stage at diagnosis are predictive of poor UDCA response (6).

From a clinical viewpoint it is key that in nonresponders causes such as nonadherence, inadequate doses, drug-drug interactions and diagnostic errors are considered prior to coming to terms with failed response to UDCA.

In a recent study nonresponders to UDCA were seen to have better survival rates when compared to untreated subjects. This suggests that UDCA benefits nonresponders beyond chemistry response (40). Therefore, "incomplete response" would be more appropriate than "nonresponse" in this setting, and maintaining UDCA therapy would be justified even in the absence of biochemical response. Hence, UDCA should not be discontinued when a second-line therapy is initiated.

UDCA has been seen to improve survival for patients with PBC. There were initially concerns regarding its impact on survival as some studies included patients treated with low-dose UDCA who were followed for fewer than 2 years, not enough time to detect differences in survival (41). When more detailed analyses were performed, excluding short-term studies (less than 2 years) and low-dose UDCA (< 10 mg/kg/day), a significant reduction in mortality rates and liver transplantation needs was positively found (42,43). This impact on survival is consistent across disease stages, but benefits are larger when treatment is started early in the course of disease. Therefore, UDCA modifies the natural history of PBC, which has contributed to a reduction in liver transplants for this condition (44,45), moreover with a cost-effective profile (46,47).

Second-line therapies for nonresponders to UDCA.

Farnesoid X receptor agonists: obeticholic acid

In recent years farnesoid X receptor agonist drugs have been developed, with obeticholic acid exhibiting the most extensive clinical development. It is a semi-synthetic bile acid with high affinity for the above receptor. It works as a key regulator of bile acid homeostasis, reducing their synthesis and increasing their biliary excretion (48). In animal models it has been seen to reduce liver inflammation and fibrosis (49), to decrease portal hypertension (50), and to improve intestinal barrier function by diminishing bacterial translocation (51,52).

Following preclinical development, the POISE clinical trial supported the drug's approval for the second-line treatment of PBC (53). As its mechanism of action differs from that of UDCA, treatment must be combined. This phase-III clinical trial enrolled nonresponder patients with PBC (93%) where UDCA was maintained or who were intolerant to UDCA (7%). The study design included 3 arms over 12 months (5 mg/day, titered up to 10 mg/day in case of lack of biochemical response at 6 months, 10 mg/day, or placebo). The primary endpoint was a composite of AP lower than 1.67 times the upper limit of normal, with reduction by at least 15%, and bilirubin decreased to below normal. A response was reached by 46% of subjects in the 5-mg arm, 47% in the 10-mg arm, and only 10% in the placebo group ($p = 0.001$), and maintained during the open-label 12-month phase (54). Overall, 34% of patients receiving 5 mg had responded by 6 months; following dose increases to 10 mg, response rates increased to 46% at 12 months. No differences in liver stiffness or symptoms were encountered. It should also be noted that biochemical response was similar in patients with and without advanced fibrosis (53). The improved chemistry induced by obeticholic acid is maintained long-term (3-6 years) (55,56), and is also associated with stable or reversed fibrosis after treatment for 3 years (57).

Pruritus was the most commonly seen adverse effect; it was dose-dependent and developed in 68% and 56% of subjects receiving 10 mg and 5-10 mg, respectively, as well as in 38% of subjects in the placebo group (53). Pruritus control strategies included bile salt-chelating resins taken 6 hours apart from obeticholic acid or antihistamins. If pruritus persists, doses should be lowered from 10 to 5 mg/day or even 5 mg every other day, or treatment could be interrupted for 10-15 days and then reinitiated at a lower dose. Other transient effects included decreased HDL and increased LDL cholesterol levels, the significance of which remains uncertain.

Obeticholic acid is the sole second-line agent licensed for the treatment of patients with PBC who are irresponsive or intolerant to UDCA. Initial dosage must be 5 mg/day, with titration to 10 mg/day when biochemical response, defined according to Paris II criteria, fails to be achieved within 6 months. The potential benefit of treatment for patients with decompensated cirrhosis (Child B and C) has not been specifically approached. If administered, treatment should be started with 5 mg/week with close

clinical and laboratory monitoring (58,59).

Fibrates

Fibrates stimulate the peroxisome proliferator-activated receptor alpha (PPARα) in hepatocytes. This activation has anticholestatic and anti-inflammatory effects (60).

In recent decades more than 30 studies, most of them non-randomized case series, have assessed the effectiveness of fibrates as second-line treatment in nonresponders to UDCA, showing significantly improved labs (bilirubin, AP, GGT). A joint analysis of these studies has been reported in two meta-analyses, which confirm lab parameter improvements when fibrates are added to treatment (61,62).

Besides these two meta-analyses, the first clinical trial (BEZURSO trial) assessing the efficacy of add-on bezafibrate in 100 patients with PBC irresponsive to UDCA has been reported of late (63). While almost 25% of patients had cirrhosis, the combination therapy normalized lab parameters (bilirubin, AP, transaminases, albumin, prothrombin time) in 30% of subjects, and managed to normalize AP alone in 67%. In addition to biochemical improvement, significant decreases in pruritus, dyslipidemia, and liver stiffness were also recorded. In contrast, no benefits were found in patients randomized in the placebo group. Tolerance was excellent with only 2 dropouts in the fibrate arm versus 6 in the placebo group. Fibrates also improve PCB dynamic prognostic indices such as the GLOBE and UK-PBC Risk Score (64).

That fibrates exert beneficial actions on two PBC characteristics such as pruritus and dyslipidemia should be highlighted. Pruritus improvement results from their anticholestatic effects, and has been seen in around 50% of patients, the effect being partly independent from biochemical response (59,63-65).

Overall, fibrates are safe and few serious adverse events have been reported. Most common are myalgia (5-10%), gastroesophageal reflux, and transient transaminase elevation. Mild increases in creatinine have been reported, likely from increased synthesis or muscular release, but without changes in glomerular filtration rate (63). Similarly, bilirubin elevations have been reported following fibrate addition in patients with PBC and cirrhosis, particularly in those with thrombocytopenia or hypoalbuminemia (66), but this effects was observed in none of the patients included

in the BEZURSO trial, where over half of patients had elastographic or histologic evidence of advanced fibrosis (63). At any rate, restricting the use of fibrates in patients with PBC and cirrhosis seems a wise thing to do, most particularly in those with evidence of hyperbilirubinemia, hypoalbuminemia, or decompensation (12,59).

The most widely used dose of bezafibrate in clinical studies is 400 mg/day, and 100-200 mg/day for fenofibrate. Although the most important study was performed with bezafibrate, no differences in efficacy have been seen between bezafibrate and fenofibrate (67). Its use in patients with PBC is not recorded in the PI of either fibrate. However, considering the extant evidence, fibrates represent a treatment option for patients with PBC irresponsive to UDCA.

Budesonide

Budesonide is a glucocorticoid that is 90% metabolized during its first liver pass, and whose affinity for the glucocorticoid receptor is 20 times higher than that of prednisolone.

Although improvements have been seen in labs and some histologic parameters, few randomized studies are available (68), hence clinical guidelines provide no specific recommendations about this drug (12,59). Also, few studies selectively enroll nonresponders to UDCA (69), and long-term effects remain unknown.

Budesonide might be useful for the treatment of patients who respond poorly to UDCA, provided they have no advanced fibrosis; however, its primary role would involve patients with overlap syndrome (primary biliary cholangitis and autoimmune hepatitis) (12,59). While fewer adverse effects occur as compared to prednisone, 20% of patients receiving budesonide had some adverse effects such as adrenal suppression, acne, mild hirsutism, and weight gain. Budesonide should be avoided in the presence of osteoporosis or blood hypertension, and is contraindicated for patients with liver cirrhosis, since lack of first liver pass metabolism results in high drug plasma levels and major adverse effects (immunosuppression, hyperglycemia) (17).

Table 3 lists the main characteristics of PBC therapies.

Liver transplant

Indications of liver transplant for PBC include decompensated cirrhosis, hepatocellular carcinoma, and intractable pruritus (12). According to the Spanish liver transplant registry of 2015, 3.1% of transplants were performed for PBC, with survival rates of 90% and 85% at 1 and 5 years, respectively. PBC recurrence post-transplant ranges from 9% to 35%, with mean time to relapse between 1.6 and 6.5 years. However, it rarely affects (< 2%) graft viability or prognosis (70,71). AMAs remain positive following transplantation, and therefore lose their diagnostic value. Consequently, PBC relapse diagnosis relies on lab changes (increased alkaline phosphatase and/or bilirubin) and compatible histology, excluding other causes such as cell rejection, ductopenic rejection, and toxicity-induced histologic lesions. Risk factors associated with disease recurrence include larger differences in age between recipient and donor, warm ischemia time, use of tacrolimus, recipient male gender, and various differences in histocompatibility antigens between donor and recipient (70,71). While some study suggested that immunosuppressive therapy with azathioprine and cyclosporin might prevent post-transplant PBC relapse, no clear evidence supports such recommendation (72). While there is no full consensus regarding the management of post-transplant relapsing PBC, European Guidelines recommend using UDCA in the presence of increased AP and/or bilirubin levels provided other causes have been ruled out (12).

OTHER TREATMENTS

Treatments have been studied for PBC that failed to show any effectiveness – colchicine, azathioprine, methotrexate, mycophenolate, cyclosporine, ustekinumab, antivirals. Nevertheless, research remains very active in PBC and newer studies are ongoing with drugs such as rituximab, CTLA-4Ig, and anti-CD40 monoclonal antibodies, as well as stem cells to modulate the immune system and regulate T-cell activity.

CLINICAL MANAGEMENT

Once the disease has been diagnosed, PBC stage (early or advanced) must be established. To this end we use biochemical parameters such as bilirubin, alkaline phosphatase, and albumin, as well as elastographic parameters to assess fibrosis

extent, with 9.6 kPa representing the best cut-off. An advantage of this noninvasive assessment of liver fibrosis is its allowing to dynamically monitor the disease, in such a way that increments of 2.1 kPa/year are associated with poorer prognosis. Treatment should be started with UDCA in weight-adjusted doses (13-15 mg/kg/day). Afterwards, treatment response should be evaluated at 6 or 12 months, which will categorize patients as *responders* or *nonresponders*. Paris II criteria are most commonly used to achieve this (Table 2). Approximately 70% of patients are responders, and for these laboratory and echo-elastographic monitoring is advised, as well as biannual DXA. In case of nonresponse (30%) potential reasons should be investigated: adherence, weight-adjusted dose, diagnostic confirmation, and drug-drug interactions. For real nonresponders second-line treatment with obeticholic acid or fibrates should be added to the ongoing regimen (Fig. 2).

CONCLUSIONS

UDCA is the pillar of medical treatment for PBC and has proven to delay disease progression and improve survival. However, around 30% of patients do not respond to this agent and have poorer prognoses, with accelerated progression and increased mortality. Therefore, it is important that these patients be identified in order to receive second-line therapies, wherein obeticholic acid represents the sole proven drug. Fibrates have promising results and also represent a valid option, particularly in patients with pruritus.

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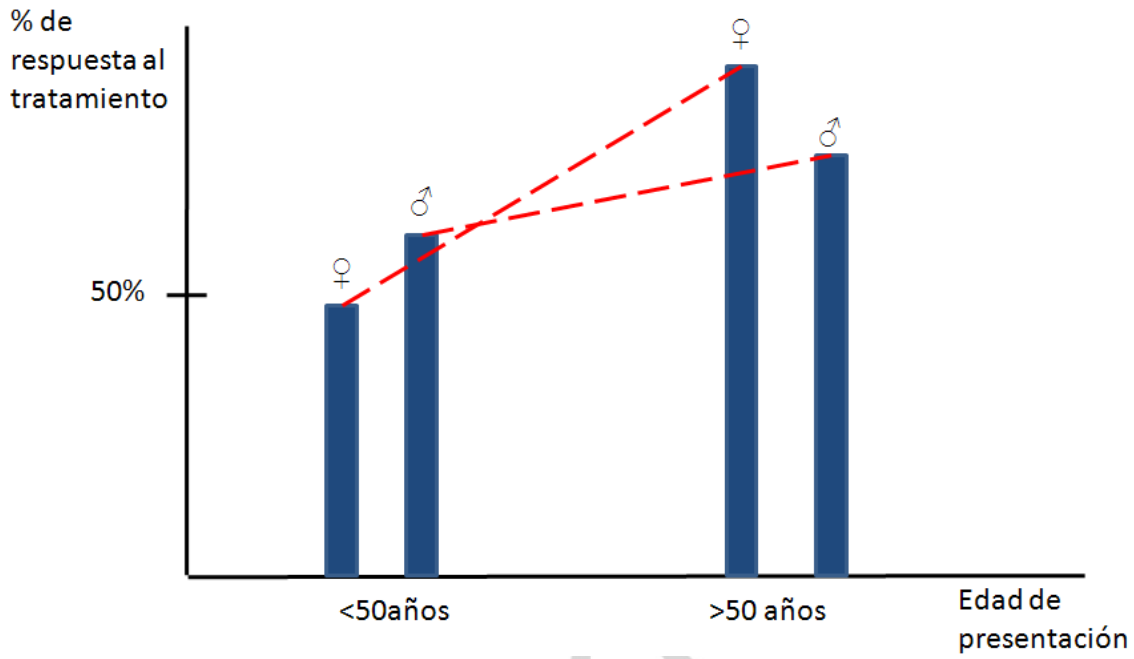

Fig. 1. Effect of age and sex on treatment response.

% de respuesta: % of response to treatment; años: years; edad de presentación: age at presentation.

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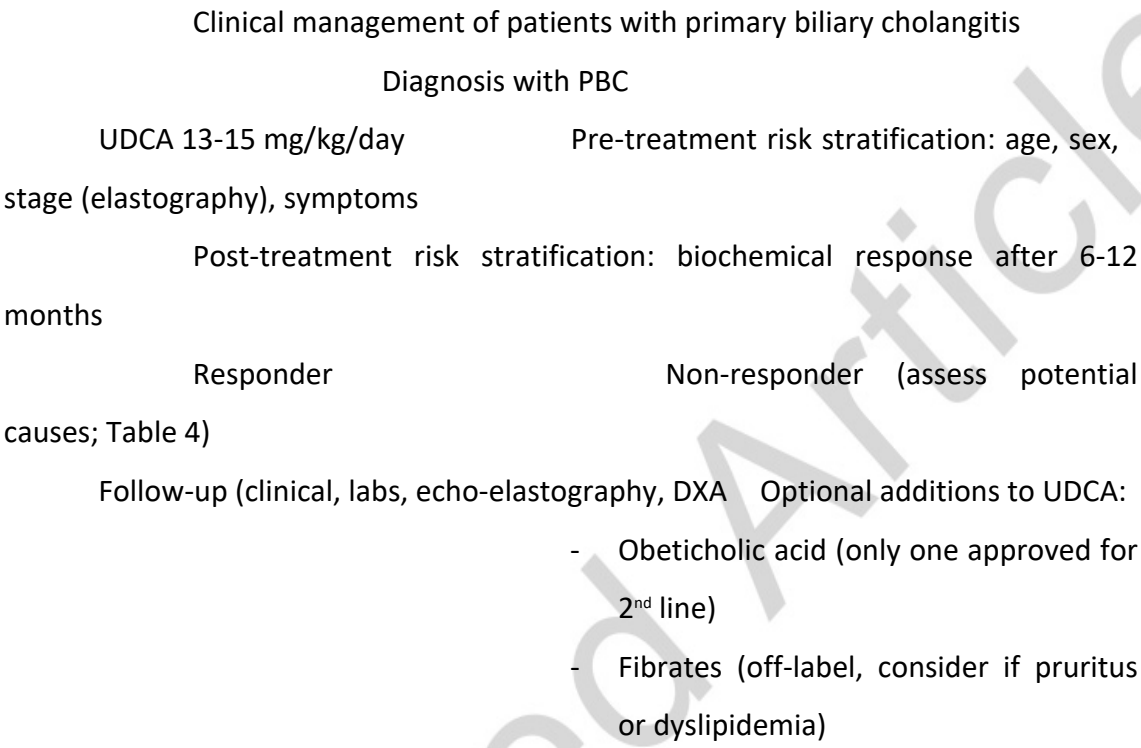

Fig. 2. Clinical management algorithm.