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Treatment of primary biliary cirrhosis

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Primary biliary cirrhosis (PBC) is a chronic liver disease of unknown etiology predominantly affecting females. It is characterized by inflammation and destruction of the intrahepatic biliary ducts and it leads to the development of chronic cholestasis. The clinical manifestations are similar to those of cirrhosis, including pruritus, jaundice, xanthomas, steatorrhea and malabsorption [1].

The disease generally affects women between 40 to 60 years of age. The age at the time of diagnosis, however, is decreasing with diagnosis being achieved earlier and in asymptomatic patients. The reason for the female predominance of 90% is unknown [2]. Primary biliary cirrhosis has been reported throughout the world. The prevalence in Western Europe is 22 cases per one million inhabitants, although this may vary from country to country and within a country. Although familial cases have been reported, there is no epidemiologic evidence that the disease is hereditary or limited to certain social or ethnic groups [3].

Scheuer classified PBC into 4 stages from a morphologic point of view [4]. In Stage I, a lesion characteristic of the biliary ducts (granuloma) may be seen. In Stage II there is ductal proliferation, hepatic fibrosis is observed in Stage III and hepatic cirrhosis in Stage IV. The stages are usually progressive and, in some cases, lesions of one or two stages may overlap. This histologic classification was later modified by Ludwig et al, and lesions were redefined as portal, periportal, septal and cirrhotic [5,6].

The initiation of the disease is variable. It may be accidently found during a routine medical examination with the observation of hepatomegaly or splenomegaly or on determining a marked increase in alkaline phosphatases or a slight rise in transaminases (in the asymptomatic forms). On other occasions, the initiation is insidious, similar to other chronic liver diseases. In certain cases, the first clinical manifestations are like those of autoimmune chronic hepatitis and in other cases they are similar to hepatic cirrhosis. The disease sometimes becomes manifest with pruritus and jaundice in pregnancy or after the consumption of oral contraceptives. In most cases, the first symptom, is pruritus which may precede the appearance of jaundice by months or even years. The initial clinical manifestations vary in length from one patient to another, until the manifestations of the different stages are presented. Jaundice, xanthomas, steatorrhea and malnutrition may also be observed.

The most common biochemical alteration of PBC is an increase in all those substances normally eliminated by the bile. Alkaline phosphatases are usually elevated, with the levels increasing with the evolution of the disease [7,8]. Other cholestatic markers, such as 5'-nucleotidase and gammaglutamyltransferase are also elevated. Bilirubin is usually normal at initiation of PBC and increases on progression of the disease. The levels of bile acids and cholesterol are usually elevated during the disease. These changes are probably due to inhibition of the hepatic lipase disease in the intitial stages and a decrease in the esterification of cholesterol in the most advanced phases [9]. A slight elevation in transaminases may be observed. Albumin and prothrombin time are usually normal in the initial stages of the disease, but may change with progression and the appearance of signs of liver failure [7,8]. Moreover, hypergammaglobulinemia, erythrocyte sedimentation rate and normocytic and normochronic anemia may be observed. In 75% of the cases, hypergammaglobulinema is a consequence of the marked increase in immunoglobulin M. Immunoglobulin G is also usually increased, while immunoglobulin A is usually normal.

One of the most important diagnostic tests is the determination of antimitochondrial antibodies (AMA) which are found in 90 to 95% of the cases of PBC. The AMA are non organospecific antibodies that react against a lipoproteidic component of the internal membrane of the mitochondria [10]. To date, 9 types of AMA have been determined and it has been demonstrated that they may be associated with several diseases, some of which are specific. Patients with PBC react with the M2, M4, M8 and M9 subtypes, with the most frequent in PBC being the M2 subtypes [11]. In addition to AMA, other non organospecific circulating antibodies, such as antinuclear [12], antithyroid and anti smooth muscle antibodies [13] may be observed.

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Treatment of PBC

Treatment of PBC is directed at improving, or preventing, the effects of chronic cholestasis and reversing the mechanism or mechanisms determining its appearance by specific treatment.

Symptomatic treatment

Patients may carry out normal physical activity while their general state allows them to do so. No special diet is required, as long as correct protein and calory intake is maintained. Moderate sunbathing is convenient and at least half a liter of milk should be ingested daily to counterbalance the deficit of intestinal vitamin D and calcium absorption. Only alcohol intake is contra-indicated.

Treatment of pruritis

Pruritus is one of the most bothersome symptoms in PBC. Many therapeutic measures have been used, among which the administration of cholestyramine and phenobarbitone are the most well known.

Cholestyramine is a resin of ionic exchange which is bound to the bile salts in the intestinal lumen impeding their absorption. It is administered orally at an intitial dose of 12 g 3 times a day [14-17], with administration at breakfast being double that of the posterior dose since the biliary vesicle is full of bile in the morning. It is therefore recommended that the dosage be divided as 4 g before breakfast, 4 g after breakfast and the remaining 4 g before to lunch. A reduction in pruritus is not usually observed for about 3 days, when the reservoir of bile salts has decreased. Cholestyramine may cause constipation and intestinal discomfort. In cases in which cholestyramine is not effective at the dosis indicated, an increase in dosage is not useful.

Phenobarbitone is a powerful enzyme inducer and cholerectic which increases bile flow, regardless of the bile salts. It is usually administered at an initial dose of 3 mg/kg of b.w. over the first 4 days, and is thereafter reduced to 50-100 mg/day in only one nightly dose. Prolonged phenobarbitone administration may produce somnolescence and alter vitamin D metabolism.

Rifampicin is an antibiotic with an intense induction capacity on the hepatic microsomal system. It significantly reduces pruritus and is much more effective than phenobarbitone [18-21]. In addition, it is accompanied by a marked decrease in alkaline phosphatase levels, transaminases and even, despite the enzymatic induction effect, by a decrease in gammaglutamyltransferase. Rifampicin may be administered over long periods with a certain amount of safety, although the transaminase levels should be monitorized for hepatotoxicity, which occurs in about 15% of the cases.

Other substances used against pruritus in PBC are opiate antagonists [22,23] (naloxone, namelfen, naltrexone), propofol [24] and S-adenosylmethionine [25].

Treatment of malabsorption

Due to a lack of bile acids in the intestinal lumen, malabsorption of liposoluble vitamins is observed. To avoid these deficiences, vitamin D should be administered as 25-hydroxycholecalciferol at a dose of 266 μg every 8-15 days. Calcium supplements such as calcium gluconate are given orally at 3 g/day, representing 1500 mg of calcium element/day [26]. Vitamin A is administered at a dose of 50,000 IU every 15 days to avoid hemeralopia or night blindness [27]. Vitamin K may be administered intramuscularly (10 mg every week) if the prothrombin time is decreased. Vitamin E is given orally at 200 mg/day to improve asthenia [28]. In some malnourished patients, medium chain triglycerides are recommended such as coconut oil extract at one soup spoon 3 or 4 times a day.

Treatment of osteodystrophy

Osteodystrophy is frequent in PBC patients, consisting of the combination of a progressive reduction in bone volume (osteoporosis) and a bone mineralization deficit (osteomalacia) [29]. The previously mentioned administration of vitamin D and calcium at the doses indicated does not always prevent the appearance of osteoporosis [30]. Since osteoporosis is fundamentally produced as a consequence of deficient osteoblastic function, sodium fluoride [31] has been studied in these patients with good results and has been found to prevent a decrease in bone mass. At present, other antireabsorption therapies such as calcitonine and dephosphonates are being studied.

Treatment of hyperlipidemia

There is currently no adequate treatment against hyperlipemia in PBC. In cases with intense neuritic pain by xanthomatous invasion of the nerve lining, plasmapheresis with activated charcoal is recommended.

Specific treatment

Several specific therapies for PBC have been studied. These treatments are usually divided into 2 groups; immunomodulators, such as corticoids, azathioprine, cyclosporin and methotrexate and other drugs which, in addition to their anti-inflammatory action, produce an antifibrogenetic effect, such as penicillamine and colchicine. The other group only includes ursodeoxycholic acid, the beneficial effect of which is due to a decrease in toxic bile acids.

Corticoids

Corticoids have an immunosuppressive effect and were first administered in 1955. In this study, promising beneficial clinical and biochemical data were demonstrated but with the disadvantage of a clear exacerbation of the metabolic bone disease. In later studies [32], similar results were observed, even with the addition of oral calcium and vitamin D supplements. That is, improvement was observed in biochemical and some histologic parameters, but with a decrease in bone trabecular volume by densitometry and seried bone biopsies. Nonetheless, the controversy regarding its use is

not as yet resolved and the results of a recent study appear to justify the indication of low dose corticoids [33]. Patients with PBC receiving a dose of prednisolone of 10 mg/day over 3 years did not show any significant differences in bone mineral content versus the control group. However, although analytical and histologic improvement was observed with corticoids, no changes were reported with respect to survival in the 2 groups.

Further information is required regarding the usefulness of second generation synthetic corticoids, such as budesonide, which has a 15-fold greater affinity for the glucocorticoid receptor. Corticoids are well absorbed in the intestine and up to 90% of the oral dose is metabolized in the liver, minimizing the secondary effects which are systemically undesirable. Another third generation synthetic corticoid which may be useful is deflazacort. However, insufficient information is available concerning its possible usefulness in PBC.

Azathioprine

Initial studies indicated that azathioprine was not effective in the treatment of PBC. In later analysis of the latest controlled trial, azathioprine was found to have a small beneficial effect on very slightly improving the survival of PBC patients [34]. This effect, however, was so small that azathioprine probably has no efficacy.

Penicillamine

Penicillamine was used after azathioprine. In addition to being a copper chelate, penicillamine has an immunosuppressive and antifibrogenetic effect. Its use, however, did not demonstrate any beneficial effect, but did produce numerous secondary effects, some of which were severe [35].

Colchicine

The use of colchicine in PBC was justified by its antiinflammatory and antifibrogenetic properties. The dosage of colchicine used is 1.2 mg/day. It causes a reduction in parameters of cytolysis and cholestasis, hyperbilirubinemia and cholesterol, increasing serum albumin. Likewise, the mortality was significantly lower in patients treated than in controls receiving placebo [36]. Despite this clear therapeutic efficacy, a long term follow up study did not show any evident improvement in the prognosis of these patients [37]. Nonetheless, no histologic improvement was observed. Further controlled studies are currently required, including a larger number of patients in order to confirm the effectiveness of colchicine in PBC.

Cyclosporine

Cyclosporine A is a powerful immunosuppressive drug that was initially studied in few patients with PBC. Although pruritus and biochemical alterations improved in the patients treated, no clear histologic evidence was found [38]. Cyclosporine A does not appear either to increase the survival or prevent the complications of PBC, which, together with its nephrotoxic and hypertensive effects, has led to its discontinuation in more extensive studies. In a more recent study, in patients with PBC, cyclosporine A increased the biochemical parameters of bone remodelling and impeded the loss of bone mass. However, in an extensive multicenter European study [39], including 349 patients, cyclosporine A was not found to improve the survival of PBC patients.

Methotrexate

The use of methotrexate at a dose of 15 mg/week over 12 months produced an improvement in clinical manifestations, biochemical parameters and hepatic inflammation [40]. Nonetheless, long term treatment is uncertain because of possible severe secondary effects such as myelosuppression, hepatotoxicity or interstitial pneumopathy. Further studies are required to confirm these hopeful initial studies.

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) increases the intrahepatic content of the hydrophillic bile acids, but decreases hydrophobic bile acids (cholic and lithocholic) which induce a hepatotoxic effect [41]. Apart from this main activity, other mechanisms of additional action are attributed to UDCA [42-46]: 1) it inhibits the intestinal absorption of endogenous bile acids; 2) it produces choleresis rich in bicarbonate; 3) it has a hepatoprotector effect, stabilizing the hepatocellular membrane; 4) it inhibits the expression of class I HLA antigens in the hepatocytes, impeding the cytotoxicity measured by T-lymphocytes, and 5) it has the capacity of developing immunomodulatory effects.

In the first pilot study in 1987, it was observed that UDCA reduced pruritus and was accompanied by a marked decrease in alkaline phosphatases and transaminases with few undesirable secondary effects, which were found to disappear on discontinuation of treatment [47]. These results led to the initiation of many controlled clinical trials. The data obtained in wide prospective studies demonstrated that UDCA is safe and well tolerated, achieving a clear improvement in biochemical parameters. The results of one multicenter study [48] confirmed the effectiveness of a dose of 13-15 mg/day of UDCA versus placebo in patients with PBC, demonstrating a significant improvement in serum bilirubin levels, alkaline phosphatases, gammaglutamyltransferase, cholesterol and immunoglobulin M. Morevoer the patients who were treated with UDCA also showed a significant decrease in the index of histologic activity, with the exception of fibrosis, which did not vary. Recent long term studies [49-52] suggest that sustained treatment with UDCA reduces the progression to the histologic lesions of PBC, prolongs patient survival or delays the indications for liver transplantation. The results of long term treatment with UDCA amplify the information of the intitial study [51]. In this study all the patients who had received placebo for 2 years were treated with the same dose of UDCA for another 2 years and the remaining patients received UDCA for 4 years. The disease progressed more slowly in those who received UDCA than in those who had received placebo. The probability of fulfilling criteria for liver transplantation or mortality was significantly lower in patients treated with UDCA than in those who re-

ceived placebo during the first 2 years. Treatment with UDCA was found to be ineffective, particularly in patients with high levels of bilirubin, and total bile acids, and low serum albumin concentration, as well as the presence of hepatomegaly and splenomegaly.

The results of a meta-analysis published based on the effectiveness of UDCA in PBC confirm the therapeutic value of this acid since an improvement was observed in the analytical and histological parameters and because the incidence of treatment failure was very low [53]. This study analyzed 5 clinical series and 7 controlled studies of patients with PBC treated with UDCA. All the trials showed a favorable effect of the treatment in transaminases, alkaline phosphatases and gammaglutamyltransferase levels, but the results in bilirubin were not homogeneous. Five of the 12 studies evaluated the effect of UDCA on histology with variable results. In 2, histologic improvement was observed, while in another 2, the changes were not significant and in the remaining study histologic deterioration was observed. The global analysis of these studies, however, concluded that UDCA has favorable histologic effects.

The results of 2 studies [54,55] showed improvement in the survival of PBC patients treated with UDCA. The first study was a meta-analysis based on 3 studies including a total of 553 patients with a mean follow up of 4 years. The other study was based on the follow up of 180 patients over 4 years. The results of these studies indicate that the patients treated with UDCA versus a placebo group, presented a significantly longer survival, in addition to a lower incidence of liver transplantation.

On the other hand, a multicenter, randomized, double-blind, study has recently been concluded in Spain [56] with the aim of investigating the effect of UDCA in PBC. In this study, no improvement was seen in survival, although an improvement was observed in the biochemical parameters of cholestasis and cytolysis as well as in histologic lesions.

Despite these hopeful results, other studies have demonstrated disease progression in patients treated with UDCA [57,58]. Therefore, in the future, the characteristics of the PBC patients who may benefit from treatment with UDCA should be established. From the data currently available, however, it appears that the best results have been achieved in patients in whom the disease has evolved little and who would have the greatest probability of reversal. Likewise, the asymptomatic patients may benefit from this treatment with the greatest guarantees of success, since prolonged UDCA treatment is not accompanied by important secondary effects and is well tolerated.

We can therefore conclude that from the present data, most PBC patients should be treated with UDCA at doses ranging from 13-15 mg/kg/day, with the exception of those patients with advanced disease who are candidates for liver transplantation, since the results in this group of subjects are not favorable.

Liver transplant

When cholestasis progresses, despite the previous therapeutic maneuvers, the only treatment possible is liver transplant. The problem in these cases is to determine the time of transplant, although most groups agree that the variables determining transplant are the levels of hyperbilirubinemia and the manifestations secondary to portal hypertension [59]. In fact, the patients with PBC with a grim prognosis, low quality of life, or both, are particularly appropriate for transplantation. It is a safe and effective therapeutic option in the advanced stages of the disease when untreatable malnutrition, pruritus or osteodystrophy or bilirubin greater than 6 mg/dl are observed. Other factors to take into account at the time of deciding transplantation are the presence of refractory ascites, bleeding from rupture of esophageal varices, spontaneous bacterial peritonitis, hepatorenal syndrome, recurrent biliary sepsis, hepatic encephalopathy or the presence of hepatocarcinoma.

Table 1. Treatment of nutritional deficiencies in primary biliary cirrhosis.

Vitamin A	50,000 IU/15 days, orally
Vitamin K	10 mg/week, i.m.
Vitamin E	200 mg/day, orally
Vitamin D	266 μg/8-15 days, orally
Calcium gluconate	3 g/day, orally
Medium chain triglycerides	20 mg/8 hours

The survival of PBC patients at one year following liver transplanation is greater than 70%, and more than 80% of the survivors achieve complete professional and social activity [60,61]. Furthermore, the survival at 5 years is greater than 75% [62].

Following liver transplantation the patients present a rapid improvement in the symptoms and complications of the disease, such as in pruritus, jaundice, encephalopathy or esophogeal varices. Unfortunately, despite treatment with calcium and vitamin D, an initial worsening is observed in osteoporosis and osteomalacia [63]. This may be related to the inactivity and the corticosteroids and other immunosuppressive therapies. Bone disease improves in prolonged survival.

The possibility of disease recurrence in the transplanted liver has been suggested [64,65], due to the reappearance of some antimitochondrial antibodies titers shortly after liver

Table 2. Criteria for indication of liver transplantation in patients with primary biliary cirrhosis.

Hyperbilirubinemia greater than 6 mg/dl
Child Pugh Grade B or C hepatic dysfunction
Bleeding by rupture of esophageal varices in Child Pugh Grade B or C
Untreatable pruritus or invalidating asthenia
Severe metabolic bone disease
Development of hepatocarcinoma
Refractory ascites
Spontaneous bacterial peritonitis
Severe hepatopulmonary syndrome
Criteria of parenchymatous liver diseases

transplantation., However, it is currently difficult to distinguish recurrence from chronic graft rejection. Both processes demonstrate nonsuppurative cholangitis with weakness of the biliary tract. Nevertheless, patients with PBC have a greater incidence of chronic rejection caused by graft failure than other patients submitted to liver transplantation.

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Juan Rodés *born in Barcelona in 1938. He studied Medicine in the Medical School of the University of Barcelona, graduated in 1962 and obtained his doctorate in 1967. Following a training period as a fellow in the University of Paris (Hôpital Saint Antoine) he became a staff member of the Hospital Clínic i Provincial. In 1968 he founded the Liver Unit in this hospital. In 1973 he was elected as Head of the Liver Unit, a post which he currently maintains. In 1985 he became a full Professor of Medicine in the University of Barcelona.*

Together whith other researchers, in 1968 he participated in the creation of the Spanish Association for the Study of the Liver, of which he was President from 1986-1989. From 1976-1979 he was a member of the Committee of the European Association for the Study of the Liver. In 1990 he was elected President of the European Association for the Study of the Liver and in 1992-1994 he became President of the International Association for the Study of the Liver. He is member of the Institut d'Estudis Catalans (1985).

Since the creation of the Liver Unit in the Hospital Clínic i Provincial of Barcelona he has initiated several linies of research together with other members of the Unit, the results of which have been published in the most prestigious international medical journals. He is author or co-author of 270 original articles, 20 books and 70 chapters published in Spain, United States, United Kingdom, France, Italy and Netherlands.

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