

REVIEW ARTICLE

MEDICAL PROGRESS

Primary Biliary Cirrhosis

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P RIMARY BILIARY CIRRHOSIS IS A SLOWLY PROGRESSIVE AUTOIMMUNE disease of the liver that primarily affects women. Its peak incidence occurs in the fifth decade of life, and it is uncommon in persons under 25 years of age. Histopathologically, primary biliary cirrhosis is characterized by portal inflammation and immune-mediated destruction of the intrahepatic bile ducts. These changes occur at different rates and with varying degrees of severity in different patients. The loss of bile ducts leads to decreased bile secretion and the retention of toxic substances within the liver, resulting in further hepatic damage, fibrosis, cirrhosis, and eventually, liver failure.

Serologically, primary biliary cirrhosis is characterized by the presence of antimitochondrial antibodies, which are present in 90 to 95 percent of patients and are often detectable years before clinical signs appear. A puzzling feature of primary biliary cirrhosis, as of several other autoimmune diseases, is that the immune attack is predominantly organ-specific, although the mitochondrial autoantigens are found in all nucleated cells. These mitochondrial antigens have been a major focus of research on primary biliary cirrhosis, which has led to their precise identification.¹ Indeed, since primary biliary cirrhosis was last reviewed in the *Journal*,² considerably more data have become available on both the autoimmune responses involved and the treatment of the disease.

CLINICAL FINDINGS

Primary biliary cirrhosis is now diagnosed earlier in its clinical course than it was in the past; 50 to 60 percent of patients are asymptomatic at diagnosis.^{3,4} Fatigue and pruritus are the most common presenting symptoms,⁵ occurring in 21 percent and 19 percent of patients, respectively, in two studies.^{6,7} Overt symptoms develop within two to four years in the majority of asymptomatic patients, although one third of patients may remain symptom-free for many years.^{4,6} Fatigue has been noted in up to 78 percent of patients and can be a significant cause of disability.^{8,9} The degree of severity of the fatigue is independent of the degree of severity of the liver disease, and there is no proven treatment for the fatigue. Pruritus, which occurs in 20 to 70 percent of patients, can be the most distressing symptom.¹⁰ The onset of pruritus usually precedes the onset of jaundice by months to years. The pruritus can be local or diffuse. It is usually worse at night and is often exacerbated by contact with wool, other fabrics, or heat. Its cause is unknown, but endogenous opioids may have a role. Unexplained discomfort in the right upper quadrant occurs in approximately 10 percent of patients.¹¹

Other common findings in primary biliary cirrhosis include hyperlipidemia, hypothyroidism, osteopenia, and coexisting autoimmune diseases, including Sjögren's syndrome and scleroderma.¹² Portal hypertension does not usually occur until later in the course of the disease. Malabsorption, deficiencies of fat-soluble vitamins, and steatorrhea are uncommon except in advanced disease. Rarely, patients present with ascites, hepatic encephalopathy, or hemorrhage from esophageal varices.¹³ The incidence of

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hepatocellular carcinoma is elevated among patients with long-standing histologically advanced disease.¹⁴ Other diseases associated with primary biliary cirrhosis include interstitial pneumonitis, celiac disease, sarcoidosis, renal tubular acidosis, hemolytic anemia, and autoimmune thrombocytopenia.

The physical examination is often normal in the asymptomatic patient, but melanin pigmentation in the skin, spider nevi, and excoriations due to itching and scratching may occur as the disease progresses. Xanthelasma are seen in approximately 5 to 10 percent of patients, but xanthomas are uncommon. Hepatomegaly is found in approximately 70 percent of patients. Splenomegaly is uncommon at presentation but may develop as the disease progresses. Jaundice is a late manifestation. Temporal and proximal limb muscle wasting, ascites, and edema occur late in the course of the disease and indicate that liver failure has occurred.

The diagnosis of primary biliary cirrhosis is currently based on three criteria: the presence of detectable antimitochondrial antibodies in serum, elevation of liver enzymes (most commonly alkaline phosphatase) for more than six months, and histologic findings in the liver that are compatible with the presence of the disease. A probable diagnosis requires the presence of two of these three criteria, and a definite diagnosis requires all three. Some hepatologists believe that a liver biopsy is not needed. However, liver biopsy allows the stage of the disease to be determined and provides a baseline for evaluating the response to treatment. As many as 5 to 10 percent of patients have no detectable antimitochondrial antibodies, but their disease appears to be identical to that in patients with antimitochondrial antibodies.

PATHOLOGICAL FINDINGS

Primary biliary cirrhosis is divided into four histologic stages. However, the liver is not affected uniformly, and a single biopsy may demonstrate the presence of all four stages at the same time. By convention, the disease is assigned the most advanced histologic stage of those present. The characteristic lesion of primary biliary cirrhosis is asymmetric destruction of the bile ducts within the portal triads (Fig. 1). Stage 1 is defined by the localization of inflammation to the portal triads. In stage 2, the number of normal bile ducts is reduced, and inflammation extends beyond the portal triads into

the surrounding parenchyma. In stage 3, fibrous septa link adjacent portal triads. Stage 4 represents end-stage liver disease, characterized by frank cirrhosis with regenerative nodules.

NATURAL HISTORY AND PROGNOSIS

In the present era, patients are more likely than in the past to be asymptomatic at diagnosis¹⁵ and to receive medical treatment earlier. As a result of treatment in earlier stages of disease, the prognosis is much better now than it formerly was. The data on survival suggesting a poor prognosis were obtained from patients in whom the disease was diagnosed decades ago, when no effective medical treatment existed. Most patients with primary biliary cirrhosis are now treated with ursodiol^{16,17};

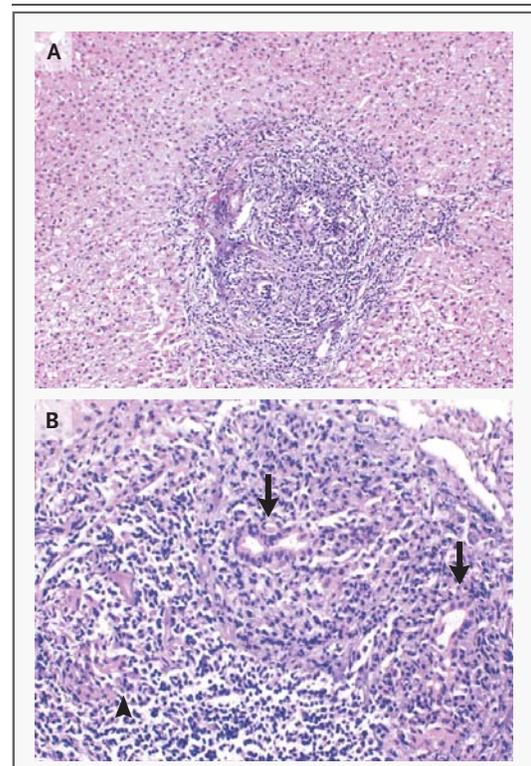


Figure 1. Bile-Duct Injury in a Patient with Stage 1 Primary Biliary Cirrhosis.

Panel A shows a damaged bile duct at the center of an enlarged portal triad that is infiltrated with lymphocytes. Panel B shows a second portal triad in the same patient. At the center and on the right side of the triad are two damaged bile ducts (arrows). On the left are the remains of a bile duct that has been partially destroyed (arrowhead). (Both panels, hematoxylin and eosin.)

other drugs that may be effective are also used.¹⁸⁻²⁰ In at least 25 to 30 percent of patients with primary biliary cirrhosis who are treated with ursodiol,²¹ a complete response occurs, characterized by normal biochemical test results and stabilized or improved histologic findings in the liver. At least 20 percent of patients treated with ursodiol will have no histologic progression over four years, and some will have no progression for a decade or longer.²² In a recent study of 262 patients with primary biliary cirrhosis who received ursodiol for a mean of eight years, the survival rate of patients with stage 1 or 2 disease was similar to that of a healthy control population, according to decision analysis with Markov modeling.²³

However, not all patients with primary biliary cirrhosis receive the diagnosis when the disease is at an early histologic stage or have a response to treatment.²⁴ For example, in the study of 262 patients with primary biliary cirrhosis, the probability of dying or undergoing liver transplantation in those with stage 3 or 4 disease, as compared with a healthy, age-matched and sex-matched population, was significantly increased (relative risk, 2.2), despite ursodiol treatment.²³ In a community-based study of 770 patients in northern England in whom primary biliary cirrhosis was diagnosed between 1987 and 1994, the median time until death or referral for liver transplantation was only 9.3 years,⁶ a survival rate no better than that predicted by the Mayo model for untreated patients with primary biliary cirrhosis.²⁵ However, only 261 of the patients in this study (34 percent) were treated with ursodiol, and those receiving ursodiol did not have improved survival. This result differs from the results of other studies.^{26,27} Furthermore, patients who were asymptomatic at the time of diagnosis did not live longer than those who were symptomatic, another difference from other studies in which asymptomatic patients lived longer than symptomatic patients.^{3,28} Factors that decreased survival were jaundice, irreversible loss of bile ducts, cirrhosis, and the presence of other autoimmune diseases. In two studies, the mean time of progression from stage 1 or 2 disease to cirrhosis among patients receiving no medical treatment was four to six years.^{22,29} In patients with cirrhosis, serum bilirubin levels reached 5 mg per deciliter (35.5 μ mol per liter) after approximately five years. Neither the presence nor the titer of antimitochondrial antibody affected disease progression, patient survival, or response to treatment.³⁰

CAUSES

EPIDEMIOLOGIC AND GENETIC FACTORS

Primary biliary cirrhosis is most prevalent in northern Europe. The prevalence differs considerably in different geographic areas, ranging from 40 to 400 per million.³¹⁻³³ Primary biliary cirrhosis is considerably more common in first-degree relatives of patients than in unrelated persons. The available data indicate that 1 to 6 percent of all patients have at least one affected family member, with mother-daughter and sister-sister combinations occurring most often.³⁴ The concordance rate of primary biliary cirrhosis in monozygotic twins is 63 percent.³⁵ However, unlike the case with other autoimmune diseases, there is little, if any, association between primary biliary cirrhosis and the presence of any particular major-histocompatibility-complex alleles.³⁶ In addition, with the possible exception of a reportedly higher risk in persons with a polymorphism of the gene for the vitamin D receptor, there are no clear genetic influences on the occurrence of primary biliary cirrhosis.^{37,38} The ratio of women to men with the disease can be as high as 10 to 1, but the disease is identical in women and men. Unlike the case with scleroderma, fetal microchimerism does not appear to have a role in the disease,³⁹ but recent data suggest that the predominance of women among patients with primary biliary cirrhosis is related to a higher incidence of X-chromosome monosomy in lymphoid cells.⁴⁰

ENVIRONMENTAL FACTORS

Molecular mimicry is the most widely proposed mechanism for the initiation of autoimmunity in primary biliary cirrhosis.⁴¹ Several candidates have been suggested as causative agents, including bacteria, viruses, and chemicals in the environment. Bacteria, in particular *Escherichia coli*, have attracted the most attention because of the reported elevated incidence of urinary tract infections in patients with primary biliary cirrhosis and the highly conserved nature of the mitochondrial autoantigens. Antibodies against the human pyruvate dehydrogenase complex react well against the *E. coli* pyruvate dehydrogenase complex. However, antibodies to the *E. coli* pyruvate dehydrogenase complex are often lower in titer and are more frequent in patients in later stages of primary biliary cirrhosis than in patients in earlier stages.

Recently, our group has studied a ubiquitous,

xenobiotic-metabolizing, gram-negative bacterium called *Novosphingobium aromaticivorans*.⁴² This bacterium attracted our attention for several reasons: it is widely found in the environment; it has four lipoyl domains with striking homology with human lipoylated autoantigens; it can be detected by polymerase chain reaction in approximately 20 percent of all people, both those with primary biliary cirrhosis and healthy persons; and it is capable of metabolizing environmental estrogens to active estradiol. Indeed, in patients with primary biliary cirrhosis, the titers of antibody against the lipoyl domains of *N. aromaticivorans* are as much as 1000 times as high as the titers of antibody against the lipoyl domains of *E. coli*; such reactivity can be found in asymptomatic patients and in those in early stages of the disease. Other bacteria have also been suggested as causative agents, including lactobacilli and chlamydia; these two bacteria have some structural homology with the autoantigen, but the reactivity against them is considerably less than that against either *E. coli* or *N. aromaticivorans*. There is a report that primary biliary cirrhosis is caused by a retrovirus resembling mouse mammary-tumor virus (MMTV),⁴³ but this work has not been reproduced.⁴⁴

Other potential causes theoretically include exposure to environmental chemicals. The liver probably evolved in part in response to the need to metabolize natural environmental substances, particularly complex foods. Recently, it was demonstrated that chemicals that mimic the pyruvate dehydrogenase complex autoepitope are recognized by circulating antibodies isolated from the serum of patients with primary biliary cirrhosis; often the affinity of the antibodies for these chemicals is greater than their affinity for the native mitochondrial antigens.⁴⁵

Many of these compounds are halogenated hydrocarbons that are widely distributed in nature and are also found in pesticides and detergents. One such halogenated compound, bromohexanoate ester, when coupled to bovine serum albumin, induces in animals a high titer of antimitochondrial antibodies that have qualitative and quantitative characteristics similar to those of antimitochondrial antibodies in humans. However, when such animals are followed for 18 months, liver lesions do not develop.^{46,47} It is unclear whether the chemical immunization is serendipitous and capable of eliciting antimitochondrial antibodies strictly on the basis of structural reactivity or whether these antimitochondrial antibodies are capable of inducing primary biliary cirrhosis.

AUTOIMMUNE RESPONSES

ANTIMITOCHONDRIAL-ANTIBODY RESPONSE

The targets of the antimitochondrial antibodies are members of the family of the 2-oxo-acid dehydrogenase complexes, including the E2 subunits of the pyruvate dehydrogenase complex, the branched-chain 2-oxo-acid dehydrogenase complex, the ketoglutaric acid dehydrogenase complex, and the dihydrolipoamide dehydrogenase-binding protein.⁴⁸ There is substantial homology among these four autoantigens, and all participate in oxidative phosphorylation and share lipoic acid moieties (Fig. 2). Most commonly, antibodies react against the pyruvate dehydrogenase E2 complex (PDC-E2); antibodies from some patients react with PDC-E2 alone, whereas antibodies from most patients also show reactivity against the branched-chain 2-oxo-acid dehydrogenase E2 complex, the ketoglutaric acid dehydrogenase E2 complex, or both. These target

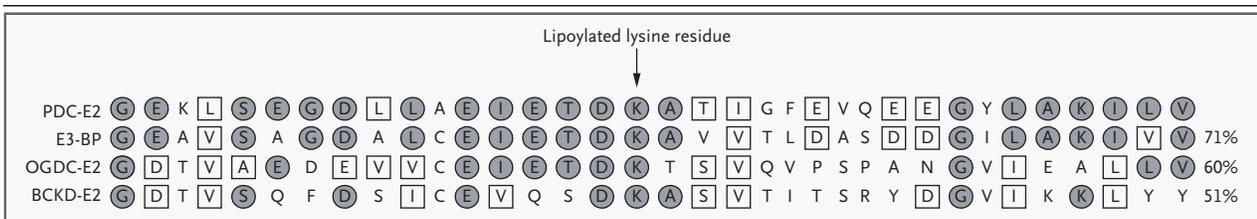


Figure 2. Lipoyl Domain Homology of Mitochondrial Antigens in Primary Biliary Cirrhosis.

There are four autoreactive mitochondrial antigens in primary biliary cirrhosis: the pyruvate dehydrogenase E2 complex (PDC-E2), E3-binding protein (E3-BP), ketoglutaric acid dehydrogenase E2 complex (OGDC-E2), and branched-chain 2-oxo-acid dehydrogenase E2 complex (BCKD-E2). The autoepitope of each autoantigen includes the region that binds lipoic acid. There is substantial homology among all four mitochondrial autoantigens. Shaded areas represent identical residues, and boxed areas conserved substitutions. The percentages of positive matches are shown on the far right.

bodies in primary biliary cirrhosis, nearly every patient with the disease, including the minority who are negative for antimitochondrial antibodies, has an elevated serum IgM level.

Although the mechanism of biliary destruction remains enigmatic, the specificity of pathological changes in the bile ducts, the presence of lymphoid infiltration in the portal tracts, and the presence of major-histocompatibility-complex class II antigen on the biliary epithelium suggest that an intense autoimmune response is directed against the biliary epithelial cells. In fact, there are reasonable data suggesting that the destruction of biliary cells is mediated by liver-infiltrating autoreactive T cells.⁴⁹⁻⁵¹

T-CELL MITOCHONDRIAL RESPONSE

The T cells infiltrating the liver in primary biliary cirrhosis are specific for the PDC-E2.^{49,50} Moreover, the frequency of the precursors of autoreactive CD4+ T cells is 100 to 150 times as high in the liver and the regional lymph nodes as in the circulation.⁵¹ The frequencies of CD8+ T cells, natural killer T cells, and B cells that are reactive with the PDC-E2 also are higher in the liver than in the blood. Indeed, the use of an extensive panel of overlapping peptides spanning the entire PDC-E2 molecule led to the identification of amino acid residues 163 through 176 (GDLLAEIETDKATI) as the minimal T-cell epitope. This reactivity is within the inner lipoyl domain and in the same region where autoantibodies bind. Phenotypically, these autoreactive T cells are positive for CD4, CD45RO, and T-cell receptor α/β and are restricted to HLA-DR53 (B4*0101). More extensive mapping studies have shown that amino acid residues E, D, and K at positions 170, 172, and 173, respectively, are essential for recognition by the T-cell clones. The amino acid K (lysine) residue is of more than passing interest, because it binds lipoic acid.

Lipoic acid has a disulfide bond that can easily be chemically altered; physically, it is on the surface of the molecule. Study of the T-cell receptor using cloned, liver-infiltrating T cells has revealed a heterogeneous repertoire. Autoreactive peripheral-blood T cells that respond to the same epitope are found only in patients in early stages of the disease, a result suggesting that progressive homing of such cells to the liver occurs along with disease progression.⁵¹ The use of major-histocompatibility-complex class I tetramers has demonstrated that CD8+ T cells specific for the PDC-E2 are 10 to 15 times as common in the liver as in the blood; these

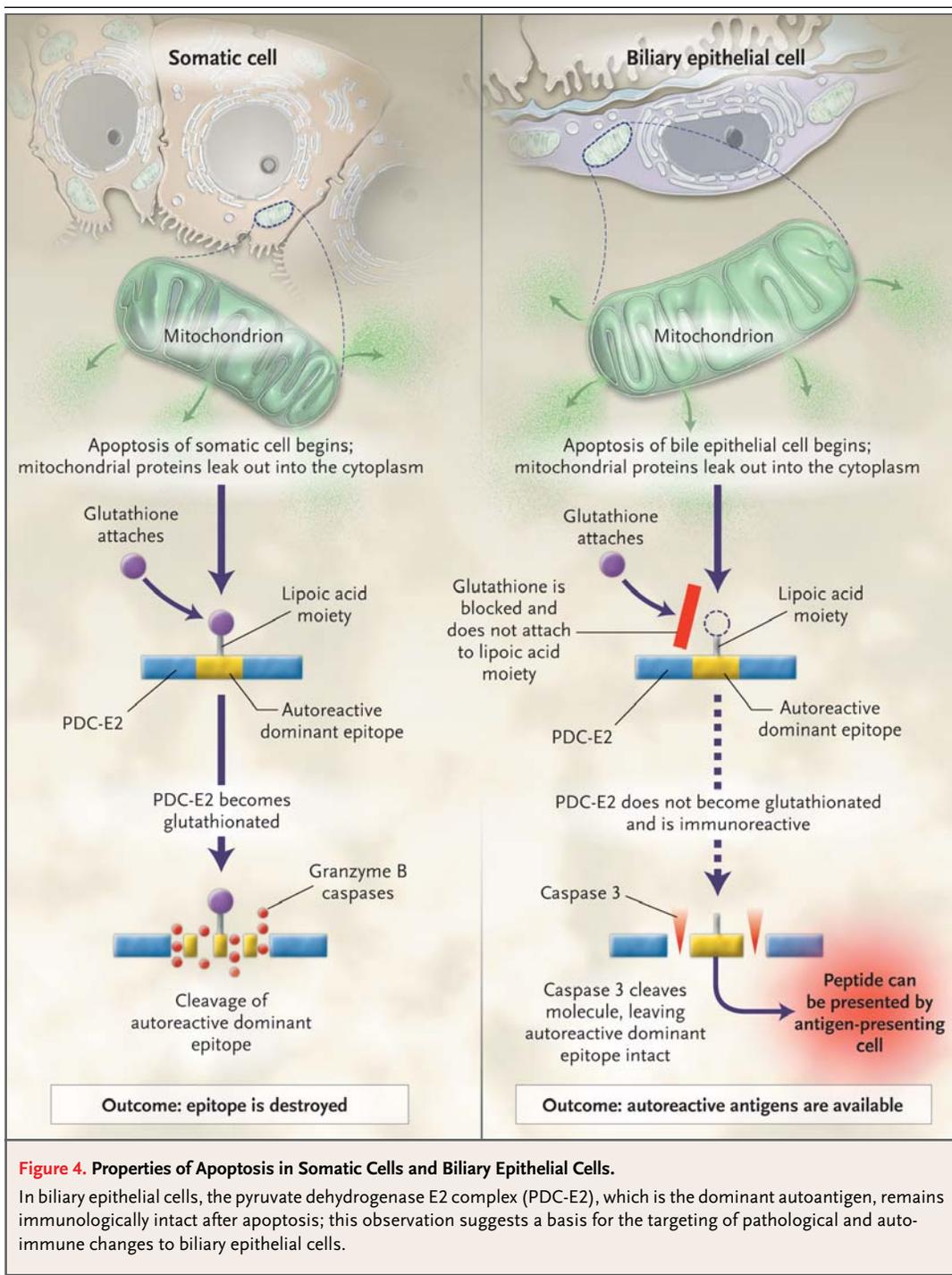
cloned CD8+ T cells produce interferon- γ in response to the PDC-E2. Extensive mapping of the HLA-A*0201-restricted epitope has demonstrated reactivity to amino acids 165 to 174 of the PDC-E2, the same region that is recognized by autoantibodies and autoreactive CD4+ T cells. This result once again points to the inner lipoyl domain and lipoic acid as critical recognition sites.

THE BILE-DUCT CELL AND APOPTOSIS

Clearly, a paradox of primary biliary cirrhosis is that mitochondrial proteins are present in all nucleated cells, yet the autoimmune attack is directed with high specificity to the biliary epithelium. It is therefore of considerable interest that there are qualitative differences between the metabolic processing of the PDC-E2 during apoptosis of bile-duct cells and its processing during apoptosis of control cells. Three recent findings suggest that these differences may be of considerable importance for understanding primary biliary cirrhosis (Fig. 4). One finding is the demonstration that the redox state of cells and, more specifically, whether the lysine-lipoyl moiety of the E2 protein is modified by glutathione during apoptosis, determines whether the PDC-E2 can be recognized by autoantibodies.⁵² The second is the demonstration that epithelial cells handle PDC-E2 in a manner different from that of other cells of the body: they do not attach a glutathione to the lysine-lipoyl group during apoptosis. Finally, specific xenobiotic modifications of the inner lysine-lipoyl domain of the PDC-E2 have been shown to be immunoreactive when tested with patient serum, again suggesting that the status of the lysine-lipoyl moiety is important.^{47,52-54} These observations suggest that the bile-duct cell is more than an innocent victim of an immune attack. Rather, it attracts an immune attack by virtue of the unique biochemical mechanisms by which it handles PDC-E2. In this respect, it should be emphasized that bile-duct cells also express a polyimmunoglobulin receptor as a possible effector mechanism, thus adding a mechanism by which autoantigen and antibody can potentially interact with the bile-duct cell targets. Clearly, much work remains to be done in this area of bile-duct immunology.

ANTINUCLEAR ANTIBODIES

Autoantibodies directed at nuclear antigens are found in approximately 50 percent of patients with primary biliary cirrhosis, and often in patients who do have antimitochondrial antibodies. The most



common antinuclear patterns are nuclear-rim and multiple nuclear dots produced by autoantibodies directed at GP210 and nucleoporin 62 within the nucleopore complex and nuclear body protein sp100, respectively. Nuclear-rim and nuclear-dot patterns are highly specific for the disease.⁵⁵

TREATMENT OF SYMPTOMS AND COMPLICATIONS

PRURITUS

Table 1 lists drugs used to treat pruritus in patients with primary biliary cirrhosis. The nonabsorbable

Table 1. Drugs Used to Treat Pruritus in Patients with Primary Biliary Cirrhosis.

Drug	Comment
Cholestyramine, colestipol	Nonabsorbed quaternary ammonium resins; dose, 8–24 g daily; effective in more than 90 percent of patients who can tolerate these drugs; 2-to-4-day delay between administration of drug and relief of itching; bound by many drugs, requiring other medications to be taken at least 2 hr before or after these resins
Rifampin	Relieves pruritus in most patients who do not respond to or cannot tolerate resins; starting dose, 150 mg twice daily; preferred to resins by many patients; may be used as initial drug to treat pruritus
Naloxone, naltrexone	Opioid antagonists; effective in some patients who do not respond to resins or rifampin
Antihistamines	Useful in patients with mild pruritus if given at bedtime to help sleep
Plasmapheresis	Usually successful when other treatments fail; used in patients awaiting liver transplantation
Metronidazole, prednisone, methyltestosterone, ultraviolet B light, cimetidine	Only anecdotal reports available

ammonium resin cholestyramine, at a dose of 8 to 24 g daily, will relieve pruritus in most patients.⁵ Rifampin, at a dose of 150 mg twice daily, is effective in patients who do not respond to cholestyramine.⁵⁶ Antihistamines may be helpful if they are given at bedtime, when the itching is not severe. The opioid antagonists naloxone and naltrexone may be effective in patients who do not respond to ammonium resins or rifampin.⁵ Plasmapheresis will usually be successful when other treatments fail.⁵⁷

OSTEOPOROSIS

Osteoporosis occurs in up to one third of patients.^{38,58} However, the severe bone disease that used to be seen, which was often complicated by multiple fractures, is now uncommon.^{59,60} There is no proven treatment for the bone disease associated with primary biliary cirrhosis other than liver transplantation. Osteopenia may worsen for the first 6 months after transplantation, but bone mineral density returns to baseline after 12 months and improves thereafter. Alendronate may increase bone mineral density, but there are no long-term studies to confirm its efficacy.⁶¹ Estrogen replacement may improve osteoporosis in postmenopausal women.⁶²

HYPERLIPIDEMIA

Serum lipid levels may be strikingly elevated in primary biliary cirrhosis,⁶³ but persons with primary biliary cirrhosis do not seem to be at increased risk for death from atherosclerosis.⁶³ Cholesterol-lowering agents are usually not needed; however, in our experience, statins and ezetimibe appear to be safe when used with appropriate monitoring.

PORTAL HYPERTENSION

In contrast to patients with other liver diseases, in whom bleeding from esophageal varices usually occurs later, patients with primary biliary cirrhosis may have bleeding early in the course of the disease, before the onset of jaundice or true cirrhosis.⁶⁴ The distal splenorenal shunt has been replaced as the preferred treatment for primary biliary cirrhosis by endoscopic rubber-band ligation and, in patients who continue to have bleeding after ligation, by a transjugular intrahepatic portosystemic shunt.⁶⁵ Survival is not adversely affected by treatment, and patients can survive for many years after variceal hemorrhage without liver transplantation.^{64,65}

TREATMENT OF UNDERLYING DISEASE

URSODEOXYCHOLIC ACID

Ursodeoxycholic acid (ursodiol), the epimer of chenodeoxycholic acid, comprises 2 percent of human bile acids and acts as a choleric agent. Ursodiol, at a dose of 12 to 15 mg per kilogram of body weight per day, is the only drug approved by the Food and Drug Administration for primary biliary cirrhosis (Table 2). It decreases serum levels of bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, cholesterol, and IgM.^{26,66} In a study that combined data from three controlled trials with a total of 548 patients,²⁶ ursodiol significantly reduced the likelihood of liver transplantation or death after four years.²⁷ Ursodiol appears to be safe and has few side effects. Some patients have weight gain, hair loss, and,

rarely, diarrhea and flatulence. Ursodiol remains efficacious for up to 10 years.⁶⁷ It delays the progression of hepatic fibrosis in early-stage primary biliary cirrhosis^{16,29} and delays the development of esophageal varices,⁶⁸ but it is not effective in advanced disease.

Two meta-analyses questioned the efficacy of ursodiol; however, these analyses were flawed by the inclusion of many studies of only two years' duration.^{69,70} Ursodiol slows the rate of progression of the disease in most patients and is highly effective in 25 to 30 percent of patients.²¹ The life expectancy of patients treated with ursodiol was similar to that of age- and sex-matched healthy controls for up to 20 years.⁷¹ However, the disease progresses in many patients, and additional medical treatment is needed.

COLCHICINE AND METHOTREXATE

Two drugs, colchicine and methotrexate, have a long history in the treatment of primary biliary cirrhosis, although their roles remain controversial. Colchicine decreased serum alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase in several double-blind prospective trials,⁷²⁻⁷⁴ but it was less effective than ursodiol.⁷³

Colchicine decreased the intensity of pruritus in two studies and improved liver histologic findings in a third⁷³⁻⁷⁵; however, other studies found no benefit of colchicine.⁷⁶ A recent meta-analysis reported that colchicine reduced the incidence of major complications of cirrhosis and delayed the need for liver transplantation.⁷⁷

Methotrexate may act as an immunomodulatory agent rather than as an antimetabolic agent at the low doses used to treat primary biliary cirrhosis (0.25 mg per kilogram per week, taken orally).⁷⁸ In some studies, methotrexate improved biochemical test results and liver histologic findings when it was added to ursodiol in patients who had had an incomplete response to ursodiol; its use was associated with sustained remission in some patients with precirrhotic primary biliary cirrhosis.^{19,20} However, other studies found no efficacy when methotrexate was used alone or in combination with ursodiol.⁷⁹⁻⁸¹ Moreover, in a 10-year-study published in 2004, survival was the same in patients taking methotrexate and ursodiol as in those taking colchicine and ursodiol,⁷⁵ and survival was similar to that predicted by the Mayo model.²⁵ One third of the patients had few signs of primary biliary cirrhosis after 10 years of treatment. No patient who was in the precirrhot-

Table 2. Drugs Used to Treat Primary Biliary Cirrhosis.

Drug	Comment
Ursodeoxycholic acid (ursodiol)	Only drug approved by the Food and Drug Administration for treatment of primary biliary cirrhosis; dose, 12–15 mg per kilogram of body weight daily; decreases serum levels of bilirubin, cholesterol, IgM, and liver enzymes; prolongs survival without liver transplantation; delays progression of liver fibrosis and development of portal hypertension
Colchicine	Used in patients who have an incomplete response to ursodiol; dose, 0.6 mg twice daily; lowers serum levels of liver enzymes and may improve survival; efficacy not proven in double-blind trials
Methotrexate	Used in patients who have an incomplete response to ursodiol and colchicine; dose, 0.25 mg per kilogram per week, orally; lowers serum levels of liver enzymes, cholesterol, and IgM and improves liver histologic findings; efficacy not proven in double-blind trials
Prednisone	Limited, if any, efficacy; worsens osteoporosis
Budesonide	Dose, 6 mg daily; improves liver histology and results of biochemical tests of liver function when used with ursodiol; no data on effects on survival
Cyclosporine	Limited efficacy; many side effects
Azathioprine, mycophenolate	Limited efficacy
Penicillamine	No efficacy; serious toxic effects
Chlorambucil	Some efficacy but serious side effects
Thalidomide, malotilate	No efficacy in small, controlled trials
Silymarin	No efficacy in pilot study; active ingredient in milk thistle; widely available in health food stores and used by many patients
Sulindac, bezafibrate, tamoxifen	Limited data available; may lower serum levels of liver enzymes

ic stage at baseline showed progression to cirrhosis.⁷⁵ Methotrexate may cause interstitial pneumonitis similar to that seen in rheumatoid arthritis.

OTHER DRUGS

Budesonide improves liver histology and the results of biochemical tests of liver function when used with ursodiol, but it may worsen osteopenia.⁸²⁻⁸⁴ Studies are of too short duration to show whether budesonide will improve survival. Prednisone has little efficacy and increases the incidence of osteoporosis.⁸⁵ Silymarin, the active ingredient in milk thistle, is ineffective.⁸⁶ Bezafibrate (a fibric acid derivative used to treat hypercholesterolemia) improved biochemical test results in a pilot study,⁸⁷ and tamoxifen decreased alkaline phosphatase levels in two women who were taking it after surgery for breast cancer.⁸⁸ Sulindac improved biochemical test results when it was added to ursodiol in a pilot study involving patients who had had an incomplete response to ursodiol.⁸⁹ Other drugs that have been evaluated but found to be either ineffective or toxic include chlorambucil,⁹⁰ penicillamine,⁹¹ azathioprine,⁹² cyclosporine,⁹³ malotilate,⁹⁴ thalidomide,⁹⁵ and mycophenolate mofetil.⁹⁶

ORTHOTOPIC LIVER TRANSPLANTATION

Liver transplantation has greatly improved survival in patients with primary biliary cirrhosis, and it is the only effective treatment for those with liver failure.⁹⁷ The survival rates are 92 percent and 85 percent at one and five years, respectively. Most patients have no signs of liver disease after orthotopic liver transplantation, but their antimitochondrial-antibody status does not change. Primary biliary cirrhosis recurs in 15 percent of patients at 3 years and in 30 percent at 10 years.⁹⁸

OVERVIEW OF TREATMENT

The optimal treatment for primary biliary cirrhosis is still uncertain. Our current approach is based on

the observation that the response to medical treatment is very variable. Each patient should be treated individually. Treatment is initiated with ursodiol. Colchicine is added if the response to ursodiol after one year is inadequate. Methotrexate is added after another year if there is an inadequate response to the combination of ursodiol and colchicine. An adequate response consists of resolution of pruritus, a decrease in serum alkaline phosphatase levels to less than 50 percent above normal, and improvement in liver histologic findings. Methotrexate is discontinued after one year if a patient does not respond to the drug. Patients who are likely to respond to colchicine and methotrexate often have serum alkaline phosphatase levels that are more than five times normal levels and intense portal and periportal inflammation.

FUTURE DIRECTIONS

The absence of an animal model of primary biliary cirrhosis has been an obstacle to research. Studies in humans, however, have clearly focused on the paradox that the autoimmune reaction is directed against ubiquitous mitochondrial autoantigens, despite the fact that the pathological changes affect primarily biliary epithelial cells. Studies have shown that post-translational modification of the PDC-E2 leads to altered host recognition. It is possible, for example, that mishandling of lysine-lipoate within these mitochondrial antigens is the pivotal event that leads to autoreactivity. It is also likely that this reaction then becomes directed at biliary epithelial cells because of the unique biochemical properties of the bile ducts, including the presence of the polyimmunoglobulin receptor on epithelial cells and the distinctive properties of apoptosis in these cell populations.

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MEDICAL PROGRESS

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CORRECTION

Primary Biliary Cirrhosis

Primary Biliary Cirrhosis . On page 1265, in Figure 3, the attachment of the acetyl group to the outer lipoyl domain in group 1 and inner lipoyl domain in group 2 is incorrectly represented. A corrected version of the figure is available with the full text of the article at www.nejm.org.