CLINICAL UPDATE

Advances in Primary Biliary Cholangitis From Digestive Disease Week 2016

Diagnosis, Treatment, and Monitoring of Patients With Primary Biliary Cholangitis

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G&H Is liver disease, particularly primary biliary liver disease, underrecognized?

FP Yes. Many Americans know some facts about the liver—for example, that it works to filter the blood, has some metabolic activity regulating glucose, produces proteins, and is a large organ. However, in one poll, 40% of individuals thought it was possible to live without a liver and that a liver was not necessary for good health.

Lack of information about the liver permeates to medical professionals as well; 2 out of 3 physicians reported that they lacked sufficient, readily available information about primary biliary liver disease. This is probably because the condition has been overshadowed by other disease states for many years.

G&H Why was the term *primary biliary cirrhosis* changed to *primary biliary cholangitis*?

FP Primary biliary cirrhosis was an unfortunate name because many patients thought that they had cirrhosis when, in fact, they did not. The name of the condition was changed to primary biliary cholangitis (PBC) because this term better reflects characteristics of the disease, including its inflammatory component, the involvement of the bile ducts, and the fact that patients may or may not have cirrhosis at the time of diagnosis. Patients also prefer the new name because of the perceived stigma surrounding the term *cirrhosis*, which many laypeople associate with alcohol use. Because of these factors, primary biliary cirrhosis is no longer the preferred nomenclature for this condition.

G&H What is the epidemiology of PBC?

FP Women are affected much more often than men, at a ratio of approximately 9:1. The age of onset can be quite variable. Many cases are diagnosed in middle-aged women, although some patients are diagnosed at a very young age. The diagnostic criteria and the regional expertise are so variable that there is a lack of consensus on many guidelines across the world. This is a progressive disease; most people are unaware that, after hepatitis C virus infection, PBC is one of the more common indications for liver transplantation in women.

G&H What is known about the pathogenesis of PBC?

FP PBC is an autoimmune cholestatic liver disease that arises when genetically predisposed individuals are exposed to an environmental trigger that sets off an immunologic cascade, causing clinical disease. Approximately 95% of patients with PBC have detectable antimitochondrial antibodies (AMAs). Patients with clinical PBC also have elevated alkaline phosphatase levels. This can be followed by loss of bile ducts, elevated bilirubin levels, and the development of fibrosis, which can lead to portal hypertension and end-stage liver disease, including the risk of developing hepatocellular carcinoma.

The likelihood of PBC developing in an asymptomatic woman with normal liver chemistries but a positive AMA test result (perhaps found incidentally) is unclear. Years ago, Dame Sheila Sherlock, who was considered the mother of hepatology, would have said that all of these

women would eventually develop PBC. However, there may, in fact, be individuals with a positive AMA test result who are not exposed to the environmental trigger and thus never develop clinical disease. Certainly, individuals with a positive AMA test result need long-term monitoring of liver chemistries.

Variations on conventional PBC have also been described. It is possible to develop PBC without a positive AMA test result, but this is very rare, and has been called different names (ie, autoimmune cholangiopathy or AMA-negative PBC).

A small percentage of patients, perhaps up to 20%, have an overlap with autoimmune hepatitis. It is important to make this distinction because PBC in these patients can progress at a much faster rate. Finally, there is a very uncommon form called premature ductopenic PBC. These individuals progress quickly to cirrhosis and end-stage liver disease, requiring a liver transplant for survival. A biopsy in these patients will reveal few remaining bile ducts. Fortunately, this is a very rare condition.

G&H How is a typical case of PBC diagnosed?

FP A typical case would be a 59-year-old woman who is referred because of an elevated alkaline phosphatase level. Her AMA test is positive, and her alkaline phosphatase level, which should typically be under 120 IU/L, is elevated at 264 IU/L. Other laboratory values, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and protein production, are normal. A biopsy shows minimal disease, with some inflammation and focal bile duct proliferation. The diagnosis of PBC would be made based upon the positive AMA test result, histologic features, and elevated alkaline phosphatase level.

G&H Is a biopsy necessary in every patient with suspected PBC?

FP Biopsy remains an important tool in the assessment of a patient with PBC. It helps to assess the clinical scenario and to determine whether any AST or ALT elevations are due to fatty liver or are autoimmune in nature. However, a biopsy may not strictly be necessary to obtain the PBC diagnosis. A positive AMA test result and an elevated alkaline phosphatase level confirmed to be of liver origin based upon a gamma-glutamyl transferase or 5'-nucleotidase test are probably enough evidence to support a diagnosis of PBC after excluding drug reactions, overt bile duct obstruction, sarcoidosis, and primary sclerosing cholangitis. However, liver biopsy remains the best way to stage the liver and rule out overlap autoimmune hepatitis.

In regard to histology, PBC is characterized by a dense portal infiltrate, numerous white blood cells (ie, lymphocytes, plasma cells, macrophages, polymorphonuclear leukocytes), and the classic feature—destruction of bile ducts. The infiltrate associated with PBC can look like a granuloma, and pathologists may describe it as granulomatous destruction of the bile ducts.

G&H What are the clinical signs of PBC?

FP The most common symptom reported by patients with PBC is fatigue, followed by pruritus. Often, the suspicion of PBC is raised based upon clinical symptoms and then followed up with appropriate tests. Patients almost universally have hyperlipidemia and may also develop lipid-rich cholesterol deposits, including xanthelasmas (smaller deposits that typically occur around the eyes) and xanthomas (larger deposits that can develop in other parts of the body). Hyperlipidemia develops because PBC interferes with normal bile salt metabolism and catabolism, which are inherently tied to the production of cholesterol in the liver. Interestingly, this type of hyperlipidemia does not predispose patients to cardiovascular disease; thus, a statin is not necessarily needed for these patients. Osteopenia is also quite common in patients with PBC.

G&H What is the role of supportive care and monitoring for patients with PBC?

FP It is important that clinicians manage the patient's quality of life as well as all of the comorbid conditions that occur with this disease. For patients with fatigue, the most common symptom, it is important to rule out or address other causes such as anemia, depression, or sleep disorders. Unfortunately, there is no simple solution if the fatigue is attributed to PBC. An exercise routine may help, as energy begets energy, but this does not tend to eliminate the problem. Stimulants such as modafinil could be an option. However, modafinil can be associated with tachyphylaxis, palpitations, and jitteriness. This approach is therefore not likely to work for the majority of patients, but it is certainly something to try.

Pruritus is a significant comorbidity in PBC and can even involve the palms and soles. Itching tends to worsen at nighttime. The pruritus associated with PBC can become quite severe, to the point where patients can even become suicidal, prompting the decision to proceed with transplantation. The etiology of PBC-associated pruritus is not well understood. Bile salts are thought to contribute, and autotoxins may be involved. Symptoms can be exacerbated by hormonal therapy, whether innate, such as with pregnancy, or exogenous.

Nonpharmacologic approaches to pruritus management include avoiding materials such as wool, which can exacerbate symptoms, and using skin moisturizers. Exposure to water can also help, as the skin does not itch under water. Taking a bath can therefore provide immediate relief from pruritus. When exiting the bath, patients should avoid towel drying, instead air drying or blotting with a towel, and then should apply moisturizer.

Several pharmacologic strategies are used for pruritus. Cholestyramine, a first-line therapy intended to sequester bile acids, is usually not an effective solution. Patients generally do not like to take cholestyramine, as it causes constipation and can interfere with the absorption of other drugs. The antibiotic rifampicin works fairly well as second-line therapy, but monitoring is required, as rifampicin can cause liver enzyme and bilirubin elevations. Opiate antagonists such as naltrexone may work reasonably well, although there is little evidence supporting this approach in the first-line or second-line setting. Serotonin reuptake inhibitors such as sertraline can have some utility, particularly in later lines of therapy after other options have proved ineffective. Overall, there are few effective options for pruritus, a symptom of PBC that is not well understood.

Clinicians should be aware of the possibility of osteoporosis in patients with PBC. Bone density studies should be performed every 2 to 3 years in these patients. Sicca syndrome, characterized by dry eyes and dry mouth, is quite common in these patients. These symptoms can lead to inadequate saliva, which can lead to dental decay.

Vitamin deficiency due to malabsorption of fat-soluble vitamins occurs in approximately one-third of patients with late-stage disease. Patients may also develop presinusoidal portal hypertension even prior to developing cirrhosis. Variceal bleeding can occur even early in the course of PBC. Thus, patients should undergo endoscopy upon diagnosis and then periodically depending upon initial findings.

Liver cancer is another potential complication of PBC. Although hepatocellular carcinoma is typically observed in patients with cirrhosis, it can also occur in noncirrhotic patients with fatty liver disease, hepatitis B virus, or hepatitis C virus. Thus, cancer surveillance is appropriate every 6 months with ultrasound and alpha-fetoprotein in patients with advanced fibrosis, even stage 3.

G&H Is there an association between symptoms and disease progression?

FP Many patients believe that their symptoms are related to disease progression. However, this is not the case, as there is no association between the development of symptoms and the natural history of the disease. This can be problematic in an asymptomatic patient who may quietly progress to cirrhosis over a 10-year span. It is therefore incumbent upon the health care provider to understand what is happening with a patient who is not complaining. If alkaline phosphatase levels continue to rise, or do not decline, the patient is most likely progressing and will eventually become cirrhotic.

G&H What is the standard treatment approach for patients with PBC?

FP The first-line treatment for patients with PBC is ursodeoxycholic acid (UDCA), a bile acid produced in humans. UDCA appears to protect the bile ducts and biliary epithelial cells from injury by altering the relative concentration of the toxic bile acids to the good bile acids. In patients with PBC, UDCA has been shown to improve alkaline phosphatase levels, reduce bilirubin, delay disease progression, and increase liver transplant–free survival.

UDCA is typically dosed at 15 mg/kg/day in 2 divided doses. Higher doses do not affect efficacy. Originally, UDCA was dosed 3 times a day. The switch to twice-daily dosing helps patient adherence.

G&H At what point in the course of disease is it appropriate to start treatment?

FP Early diagnosis and initiation of treatment as soon as possible are crucial for maximizing outcomes in patients with PBC. Patients who start treatment early have similar survival over a 10- to 15-year period as the general population. In contrast, late initiation of therapy is associated with very poor survival.

Some clinicians may not initiate treatment in patients who are asymptomatic or have an alkaline phosphatase level that is only slightly elevated. This is the wrong approach, as these are the patients in whom treatment is likely to have the greatest impact. If treatment is started only when patients are symptomatic or have quite a bit of fibrosis, outcomes may not be as good.

G&H How is treatment response assessed?

FP There is a lack of consensus on this issue. Alkaline phosphatase is considered to be a critical biomarker, as a lower alkaline phosphatase level is considered a surrogate for reduced bile duct damage. Clinicians, therefore, must monitor alkaline phosphatase levels in patients who are receiving UDCA.

In patients with advanced disease, improved bilirubin is certainly considered beneficial. However, there should

be emphasis on treating patients prior to the development of jaundice, at which point there is a low likelihood of long-term survival.

Guidelines from the American Association for the Study of Liver Diseases, which were released in 2009, do not define treatment success, although they consider alkaline phosphatase levels to be the most important metric. Various European guidelines recommend assessing alkaline phosphatase levels after a year but diverge on the definitions of treatment success. The Barcelona criteria require a 40% decrease or normalization of alkaline phosphatase levels, and earlier Paris criteria required a reduction in alkaline phosphatase levels to less than 3 times the upper limit of normal. Toronto and the second-generation Mayo Clinic guidelines use an alkaline phosphatase level less than 1.67 times the upper limit of normal, whereas the modified Paris criteria require less than 1.5 times the upper limit of normal. A cutoff between 1.5 and 1.67 times the upper limit of normal is likely to stick, as it is based upon data suggesting better outcomes with this degree of response.

Whether AST and ALT levels normalize depends upon the presence of overlap syndromes. Patients with autoimmune liver disease or hepatitis can introduce variability, as can concomitant fatty liver, which occurs with many of these patients.

G&H What proportion of patients respond to current therapy?

FP Current treatment works in approximately 60% to 70% of patients. Therefore, up to 30% to 40% of patients do not respond to UDCA, and there is still a need for new therapeutic strategies for patients with PBC.

This column is based on a Digestive Disease Week 2016 presentation sponsored by Intercept Pharmaceuticals.

Dr Poordad is an advisor and speaker for Intercept, Salix, and Valeant Pharmaceuticals.

Suggested Reading

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