

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Current and Future Therapy for Primary Sclerosing Cholangitis

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G&H Could you discuss the current understanding of the pathophysiology of primary sclerosing cholangitis (PSC)?

FM The pathophysiology of PSC remains poorly understood. Several theories have been proposed, as no specific mechanisms have been pinpointed. There is increasing evidence of a genetic predisposition to PSC, but the exact mechanism of susceptibility has not been well defined as of yet. In patients who are genetically predisposed, there are most likely several triggering factors, such as infectious agents or exotoxins that may initiate the disease. In addition, immune-mediated mechanisms are also evident, as patients with PSC have increased circulating autoantibodies in the serum, and cytotoxic factors may induce an inflammatory response that leads to destruction of bile ducts and becomes perpetuated in genetically predisposed patients.

G&H How prevalent is PSC in the general population and in patients with inflammatory bowel disease (IBD)?

FM In the general population, the prevalence of PSC has not been very well defined. A recent population-based study conducted by Mayo Clinic found a prevalence of 13.6 per 100,000. However, various studies have reported the prevalence of PSC in the general population to range anywhere from 4 to 15 per 100,000 individuals, though the rates differ according to geography and the year the study was conducted. Diagnostic procedures have improved since the time that many of these studies were conducted.

The prevalence of PSC is higher among patients with IBD. Approximately 5% of patients with IBD also suffer from PSC, an association that is more common in patients with ulcerative colitis as opposed to Crohn's disease. When looking at patients with PSC, IBD has an even higher prevalence: up to 70% of patients with PSC will develop IBD.

G&H Could you discuss the main medical, endoscopic, and surgical treatment options for PSC?

FM The treatment options for PSC are very limited. The only curative option that is currently available is liver transplantation. Several drugs have been investigated for PSC, but none, unfortunately, has shown any benefit in slowing disease progression. Although initial studies of ursodeoxycholic acid showed improvement in biochemical and several clinical parameters, ursodeoxycholic acid has been shown not to decrease the need for liver transplantation or to offer any survival benefit, at least at the standard dosage. Nevertheless, in clinical practice, many physicians offer ursodeoxycholic acid as an empiric treatment to patients with PSC because of a lack of medical alternatives and the positive safety profile associated with the medication.

Various immunomodulatory and antifibrotic agents, including steroids, azathioprine, methotrexate, etanercept, pentoxifylline, and penicillamine, to name a few, have also been investigated for the treatment of PSC, but studies have not shown them to be helpful across the board. Therefore, they are not indicated for the treatment of patients with PSC.

Endoscopic therapy is not routinely performed for treatment of PSC, unless there is a dominant stricture causing jaundice and related symptoms. Dominant strictures are not very common, but when they occur, they are usually treated with balloon dilation. The other treatment option involves stents, but they are associated with increased complications and thus not usually the preferred choice. When dominant strictures develop, it is important to exclude the development of cholangiocarcinoma, one of the most serious and feared complications of PSC.

There are no surgical options for the treatment of PSC other than liver transplantation. Surgery is usually avoided in these patients, unless they have an isolated extrahepatic stricture that would be amenable to surgical therapy and very early-stage disease (ie, they do not have cirrhosis or advanced fibrosis).

G&H What are the outcomes of liver transplantation in patients with PSC? Are there any contraindications to transplantation in this patient population?

FM Liver transplantation is associated with excellent outcomes for patients with PSC, which is the fifth leading cause of liver transplantation in the United States. The survival rates are impressive: the 1-year survival has been reported at 90–97%, and 5-year survival at 85–88%. Nevertheless, there are some increased risks for liver transplantation in patients with PSC compared to those with other indications for transplantation. Patients with PSC may have increased acute and/or chronic rejection. In addition, these patients are more prone to develop hepatic artery thrombosis, and there is a recognized risk of recurrence after transplantation, which may affect the outcome. Although these risks should be taken into account, PSC is considered an excellent indication overall for transplantation.

Cholangiocarcinoma is considered a contraindication to liver transplantation by most centers. Some centers such as Mayo Clinic have reported good liver transplantation results in very carefully selected patients. However, for the most part, patients with cholangiocarcinoma are not considered candidates.

G&H What are the treatment options for the various complications associated with PSC?

FM PSC is associated with numerous complications, including pruritus. Physicians have several treatment options available and usually start with antihistamines. Other options include cholestyramine, rifampicin, or opioid antagonists. Recently, a study was published regarding the use of the selective serotonin reuptake inhibitor

sertraline that showed promising results. The results of therapy with these different agents can vary considerably in terms of patient response. Sometimes the pruritus can be so severe and nonresponsive to any of these therapies that there is an indication for liver transplantation.

As bone disease is a very common problem in patients with PSC, periodic screening with bone-density scans should be performed, and supplementation with calcium and vitamin D is recommended. Once evidence of osteopenia or osteoporosis is found, the patients can be treated with bisphosphonates, or hormone-replacement therapy in women.

Other complications that patients with PSC are prone to develop include cholangitis (which can be treated with antibiotics), dominant strictures, gallstones, and common bile duct stones (sometimes requiring endoscopic treatment).

Cholangiocarcinoma, as mentioned previously, is the most serious complication. Patients with PSC have a lifetime risk of 7–15% of developing cholangiocarcinoma, with a yearly risk of approximately 0.5–1%. Thus, it is important to be aware of this potential complication, even though there are no screening guidelines for this type of cancer and treatment options are extremely limited.

G&H Could you discuss the relationship between PSC and colorectal cancer and whether treatment of PSC reduces the risk of this cancer?

FM In patients with PSC, the risk of colorectal cancer is markedly increased. Patients with ulcerative colitis alone already have an increased risk of colon cancer. If patients have both ulcerative colitis and PSC, their risk is almost 5 times higher compared to those with ulcerative colitis alone. Thus, it is very important that these patients receive yearly surveillance with colonoscopy and random biopsies to exclude the development of colon cancer.

As for the theory that treating PSC decreases the risk of colorectal cancer, no evidence has demonstrated this association, even in the posttransplantation setting. There have been some studies showing that ursodeoxycholic acid may decrease the risk of developing cancer, but that association is not definite either.

G&H Could you explain the implications of the study you conducted on elevated serum immunoglobulin (Ig)G4 concentrations in patients with PSC?

FM In this study, my colleagues and I evaluated the concentration of IgG4 in the serum of patients with PSC and found it to be elevated in approximately 9% of our cohort of patients. This finding was significantly

higher than in primary biliary cirrhosis (PBC) patients, in whom we did not find any evidence of elevated IgG4 levels. Patients with elevated IgG4 levels also had some parameters of liver disease severity that were more pronounced, such as higher levels of alkaline phosphate, total bilirubin, and PSC Mayo risk scores. We also found that patients with elevated IgG4 levels had a shorter time to require liver transplantation, a median time of 1.7 years versus 6.5 years for patients with normal IgG4 levels.

Elevated IgG4 levels are a marker of autoimmune pancreatitis, and some patients with this condition have been known to have cholangiographic findings very similar to those of patients with PSC. Our study left us wondering whether the patients with elevated IgG4 levels were true PSC patients or whether these were patients with a different type of disease (such as autoimmune pancreatitis without obvious pancreatic findings) that we were not diagnosing. It was suggested that steroids may be helpful in this setting, as they are very helpful in patients with autoimmune pancreatitis. The next steps for this study would be to consider clinical trials with steroids in patients with elevated IgG4 levels, even though the prevalence of the elevated levels is not very high.

G&H What do you foresee as the future for PSC therapies?

FM For the development of new therapies, it is critical that we improve our understanding of the pathophysiology of PSC; as our knowledge of the mechanisms involved in the biliary inflammation and destruction in

PSC increases, we will be able to better target therapies to treat this disease.

Researchers are also looking into high-dose ursodeoxycholic acid (20–30 mg/kg daily) as a potential therapy, as the standard dose used to treat PBC has not shown definite benefits in patients with PSC, but preliminary results showed biochemical and clinical improvement. We are awaiting the final results of this trial.

Another clinical trial, evaluating the effects of docosahexaenoic acid, is underway. This agent has anti-inflammatory properties, which are in part due to its agonistic effects on peroxisome proliferator-activated receptors.

In addition, in a very small study, bezafibrate showed some biochemical improvement in patients with PSC, and larger additional studies may be warranted.

Suggested Reading

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