ANNALS OF GASTROENTEROLOGY 2006, 19(2):158-162

Lecture

Extraintestinal manifestations of Inflammatory Bowel Diseases: Is there effective liver therapy?

J. Vlachogiannakos

SUMMARY

Hepatobiliary diseases are common in IBD patients, including primary sclerosing cholangitis, sclerosing cholangitis of the small bile ducts, cirrhosis, cholangiocarcinoma, fatty liver and cholelithiasis. PSC is the most common of these diseases, with an incidence ranging from 2.5% to 7.5%. It usually progresses insidiously and finally leads to cirrhosis independent of inflammatory bowel disease activity. The probability of cholangiocarcinoma is very high in PSC patients and the prognosis is dismal. There is an elevated risk of developing colon cancer in patients with PSC. Medical therapy has not proven successful in slowing disease progression or prolonging survival in PSC. Endoscopic therapy is recommended for treating complications of recurrent cholangitis or worsening jaundice in cases of dominant stricture, but these approaches have not been definitely demonstrated to improve survival or decrease the need for liver transplantation. Liver transplantation remains the therapy of choice for patients with advanced liver disease.

INTRODUCTION

The hepatobiliary system and the gastrointestinal tract are closely linked embryologically and thus the liver is vulnerable to the development of complications of many gastrointestinal diseases, particularly inflammatory bowel disease (IBD). The prevalence of liver disease in patients with ulcerative colitis (UC) and Crohn's disease (CD) varies widely in different series. Abnormal liver function tests are found in almost half of patients with IBD requiring surgery and are associated with malnutrition, sepsis, total parenteral nutrition and blood transfusions which increase the risk of viral infections. It is believed that approximately 5% of adult patients with IBD will develop significant hepatobiliary disease.[1] Moreover, severe significant liver disease is more commonly seen in patients with UC and when it occurs in CD it is usually associated with extensive colonic involvement. It is now well accepted that the major hepatobiliary diseases seen in association with IBD, namely primary sclerosing cholangitis, pericholangitis, cirrhosis, cholangiocarcinoma and rare cases of autoimmune hepatitis represent different aspects of the same spectrum of liver disease.

2nd Department of Gastroenterology, Evangelismos Hospital, Athens

Author for correspondence:

John Vlachogiannakos, 24 Iraklidon str., 141 21 Athens, Greece, tel.: +210-7201609

PRIMARY SCLEROSING CHOLANGITIS (PSC)

PSC is a progressive cholestatic liver disease characterized by intrahepatic and extrahepatic biliary duct fibrosis as well as associated inflammatory changes involving the portal and periportal regions of the liver. It is more frequent in male individuals and the prevalence of IBD (mostly UC) in PSC is about 70-80%. Conversely, about 2-7% of UC patients[2] and 0.7-3.4% of CD patients[3] have a diagnosis of PSC. The clinical presentation of PSC is variable, but usually includes fatigue, intermittent jaundice, weight loss, right upper quadrant abdominal pain and pruritus. Some patients with PSC may present with an established cirrhosis and portal hypertension without any previous symptoms of cholangitis or cholestasis. There are no specific auto-antibodies and so biopsy or cholangiography is often necessary for the diagnosis. The outcome of the hepatobiliary disease is completely unrelated to the activity, severity, or clinical course of the colitis. Indeed, liver disease may develop some years after a total colectomy has been performed.

A minority of patients with UC will have persistently

abnormal liver function tests, together with histological appearances, such as concentric fibrosis, but have normal bile ducts at cholangiography. The term "small-duct primary sclerosing cholangitis" has been proposed to replace the term "pericholangitis" in this group of patients as the evidence suggests that these conditions are all part of the same disease spectrum.

The treatment of PSC has been limited by uncertainty about its cause. As yet, no medical therapy has been proved effective. However, a plethora of medical, endoscopic and surgical approaches have been advocated. The treatment of PSC can be divided into the management of cholestasis, the management of complication and specific treatment of the underlying disease process.

Management of cholestasis

Pruritus is one of the more bothersome symptoms of patients with PSC. Itching is worse at bedtime and in warm weather and may be exacerbated by eating rich, fatty meals. Cholestyramine in a dose of 4 to 8gr taken two or three times daily is usually effective.[4] Other therapies that have used in patients unresponsive to cholestyramine include naloxone, Phenobarbital, rifampin, plasmapheresis, ondansetron, antihistamines and ultraviolet light. Steatorrhea and malabsorption of fat-soluble vitamins may occur late in the course of the disease. Vitamin deficiencies should be replaced by monthly intramuscular injections. Osteoporosis is a frequent complication of advanced PSC. Bisphoshates with calcium and vitamin D supplements should be considered in patients with osteoporosis and advanced cholestasis.

Management of complications

Antibiotics have no role in slowing the progression of PSC but have been used to treat recurrent episodes of cholangitis. Dominant strictures of the extrahepatic bile ducts which cause or exacerbate symptoms occur in 15 to 20% of patients with PSC. They can be treated endoscopically by balloon dilatation or by placing a stent across the affected area.[5] Some non-cirrhotic PSC patients may be best managed by a bilio-enteric by pass. The development of small biliary stones and sludge may lead to sudden clinical or biochemical deterioration. In these patients, endoscopic sphincterotomy with extraction of biliary debris is beneficial. In a recently published prospective trial,[6] 106 PSC patients were treated with 750mg of ursodeoxycholic acid (UDCA) per day for up to 13 years along with balloon dilatation of major dominant strictures or placement of biliary stents whenever necessary. This combined approach significantly improved overall survival rates compared with predicted values.

Specific therapy of the disease

The treatment of PSC has included uncontrolled trials of corticosteroids, immunosuppressive drugs, and stimulators of biliary secretion either alone or in combination. The results have been almost disappointing, although assessment of treatment is difficult because the clinical course fluctuates, survival is variable and some patients remain asymptomatic for long periods of time.

Ursodeoxycholic acid (UDCA): The hydrophilic bile acid UDCA has been widely used in the treatment of cholestatic liver diseases. Randomized controlled trials showed that UDCA at doses 10-15mg/kg/day improved serum liver tests and bilirubin but had no effect on symptoms, histology or survival.[7] A pilot study from Oxford has demonstrated that a higher dose of UDCA, namely 20mg/kg/day, may be efficacious in delay progression and prolong survival. No significant side effects were noted and no worsening of underlying colitis.[8] These results supported by other studies demonstrated that biliary enrichment of UDCA increases with increasing dose and reaches a plateau at 22-25mg/kg/day.[9] However, the largest and most recent trial including 219 PSC patients, found no statistically significant beneficial effect of a higher dose of UDCA (17-23mg/kg/day) than that previously used on survival or prevention of cholangiocarcinoma in PSC.[10]

Immunosuppressive agents: The role of corticosteroid therapy in PSC remains unclear. There have been no controlled trials of steroid therapy, although most patients have been exposed to courses of corticosteroids when they are prescribed for their coexistent UC, and these courses have not been found to have any impact on their liver disease. Corticosteroids have been used both topically and systemically in small trials without a significant improvement in the course of the disease.[11] Some trials have used budesonide which has a high first pass metabolism to avoid the side-effects of long-term use of corticosteroids, particularly osteoporosis.[12] A number of immunosuppressive agents have been tried either alone or in combination including penicillamine, methotrexate and cyclosporine. No benefit has been demonstrated.

CHOLANGIOCARCINOMA (CCC)

CCC develops in 6-20% of patients with long standing PSC at a rate of 1-5% per year. The clinical presentation of bile duct cancer is that of a progressive cholestatic jaundice.[13] Cholangiography usually reveals a particularly narrow bile duct stricture. The tumor usually pursues a progressive course and the prognosis is very

poor, with a median survival of 9 months. Endoscopic treatment is usually the best palliative option once the diagnosis of established CCC has been made. Liver transplantation for isolated CCC occurring in PSC has been disappointing with rapid recurrence of tumor.[14] Nevertheless, in patients who might be suitable for liver transplantation, biliary manipulation is best avoided as it increases the risk of structuring and bacterial cholangitis and may preclude the chance of successful transplantation.

CIRRHOSIS

The incidence of cirrhosis in patients with IBD is varied in different series between 1% and 5%. The majority of these patients will have underlying end-stage PSC. All the usual complications of decompensated cirrhosis, including oesophageal and gastric varices, ascites and porto-systemic encephalopathy are seen in the advanced stages of PSC and the management of these is the same as for any cause of cirrhosis.[15] Patients with concomitant IBD who have undergone total proctocolectomy may develop peristomal varices which are complicated with severe and difficult to manage bleeding.[16] Local treatment with injection of sclerosant, venous ligation and ileostomy revision are often unsuccessful. Porto-systemic shunts, i.e. TIPS can be useful in this situation or, alternatively this may be an indication for liver transplantation.

LIVER TRANSPLANTATION

Orthotopic liver transplantation (OLT) is the only long-term treatment for patients with PSC and advanced liver disease. However, the optimum timing for transplantation is made difficult by the variable clinical course of PSC and the potential risk of CCC. Transplantation earlier in the course of the disease reduces the operative risk and the risk of the development of hepatobiliary malignancy, but PSC recurs in the graft and colon cancer is a major cause of death in PSC patients after OLT. Indications for OLT are summarized in Table 1.[17] Survival rates for patients transplanted for PSC without evidence of CCC are comparable to those achieved in patients with PBC and autoimmune hepatitis, with most series publishing 5-year survival rates of 85%-90%. Where CCC is found incidentally in the explanted liver with no spread to regional lymph nodes, the prognosis is comparable with patients without CCC.[18] Clinically apparent CCC is considered a contraindication to transplantation as the tumor rapidly recurs post-transplantation. All patients referred for consideration of OLT should undergo colonoscopy to diagnose and assess the severity of underlying IBD. Patients with colitis or evidence of dysplasia should be considered for colectomy prior to, or even during OLT in view of the risks of deterioration in control of IBD post-transplant and colorectal malignancy.

PSC recurs in the liver graft in as many as 20-40% of cases and can be difficult to distinguish from biliary strictures associated with the transplant operation itself.[19] The prognosis of recurrent PSC in the allograft has traditionally been thought to be favorable in reports with follow-up periods of up to 5 years. However, several patients have required re-transplantation for advanced recurrent disease and this must now be considered a significant cause of late graft loss.

COLORECTAL CANCER IN PATIENTS WITH IBD AND PSC

It has been suggested that the risk of colon cancer is significantly higher in UC associated with PSC, with 31% of patients in one study developing colonic neoplasia at 20 years after the diagnosis of UC as compared with 5% of patients with UC alone.[20] It seems that PSC is an independent risk factor for developing colorectal cancer. Genetic predisposition, alterations in the bile salt pool due to cholestasis, and folate deficiency have been considered as possible mechanisms for the increased susceptibility to neoplasia. Thus, yearly colonoscopy is recommended in patients with UC and PSC. It has been postulated that UDCA may have a role in preventing colonic neoplasia. In the largest study to date, published only in abstract form,[21] included 120 patients with UC and PSC. A small reduction of the risk of dysplasia and cancer was demonstrated in the UDCA-treated group which failed to reach significance. However, the results of the most recent study were more promising[22] and found the use of UDCA in 59 patients with PSC and UC to be associated with a significantly lower risk for developing dysplasia.

MISCELLANEOUS HEPATOBILIARY DISORDERS ASSOCIATED WITH IBD

Steatosis has been described in more than 30% of patients but there is no evidence that the lesion progresses to chronic liver disease.[23] Treatment of the underlying bowel disorder and improvement in the general health of the patient will probably result in a resolution of the fatty change. Also cholelithiasis is more frequent in IBD patients (about 10%) than in the general population (7%) and mainly in Crohn's disease (usually localization). It

has been shown to be less symptomatic than in the general population. Liver abscesses are rarely reported in association with IBD. They are often multiple and are associated with a high mortality. Streptococci are the most frequent organisms isolated from the abscesses. Hepatic amyloidosis is a rare complication, occurring in less than 1% of patients with IBD. It is much more commonly associated with Crohn's disease than UC. Aggressive anti-inflammatory treatment of the intestinal lesions probably reduces the chance of developing systemic amyloid. Although regression of amyloidosis has been reported after colectomy, in the majority of patients the prognosis is poor.

Granulomas are occasionally seen in the liver biopsy specimens of patients with Crohn's disease. They are found in 3% to 4% of liver biopsies from patients with PSC. There have been a few case reports of autoimmune hepatitis, PBC and Budd-Chiari syndrome in patients with IBD. Finally, drug hepatotoxicity is a rare cause of hepatic injury in the context of IBD with sulfasalazine and azathioprine all having been implicated.

Table 1. Indications for liver transplantation in primary sclerosing cholangitis

1. Cirrhosis complicated by:
   - Intractable ascites
   - Variceal hemorrhage uncontrolled by endoscopic therapy
   - Muscle wasting
   - Recurrent bacterial peritonitis
   - Porto-systemic encephalopathy
2. Intractable itching or fatigue
3. Recurrent cholangitis
4. Jaundice which cannot be treated endoscopically or medically
5. Hepatocellular carcinoma (if no metastases and tumor is within accepted size)
6. Biliary dysplasia or cholangiocarcinoma *in situ*

REFERENCES

1. Talwalkar JA, Lindor KD. Primary sclerosing cholangitis. Inflamm Bowel Dis 2005; 11:62-72.
2. Olsson R, Danielson A, Jarnerot G, et al. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. Gastroenterology 1991; 100:1319-1323.
3. Rasmussen HH, Fallingborg JF, Mortensen PB, et al. Hepatobiliary dysfunction and primary sclerosing cholangitis in patients with Crohn's disease. Scand J Gastroenterol 1997; 32:604-610.
4. Lee YM, Kaplan MM. Primary sclerosing cholangitis. N Engl J Med 1995; 332:924-933.
5. Cullen SN, Chapman RW. Current management of primary sclerosing cholangitis. Aliment Pharmacol Ther 2005; 21:933-948.
6. Stiehl A, Rudolph G, Kloters-Plachky P, et al. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. J Hepatol 2002; 36:151-156.
7. Paumgartner G, Beuers U. Mechanisms of action and therapeutic efficacy of ursodeoxycholic acid in cholestatic liver disease. Clin Liver Dis 2004; 8:67-81.
8. Mitchell SA, Bansi DS, Hunt N, et al. A preliminary trial of high-dose ursodeoxycholic acid in primary sclerosing cholangitis. Gastroenterology 2001; 121:900-907.
9. Rost D, Rudolph G, Kloeters-Plachky P, et al. Effect of high-dose ursodeoxycholic acid on its biliary enrichment in primary sclerosing cholangitis. Hepatology 2004; 40:693-698.
10. Olsson R, Boberg KM, Schaffalitsky de Muckadell O, et al. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: A 5-year multicenter, randomized, controlled study. Gastroenterology 2005; 129:1464-1472.
11. Boberg KM, Egeland T, Schrumpf E. Long-term effect of corticosteroid treatment in primary sclerosing cholangitis patients. Scand J Gastroenterol 2003; 38:991-995.
12. Van Hoogstraten HJ, Vleggaar FP, Boland GJ, et al. Budesonide or prednisone in combination with ursodeoxycholic acid in primary sclerosing cholangitis: a randomized double-blind pilot study. Belgian-Dutch PSC Study Group. Am J Gastroenterol 2000; 95:2015-2022.
13. Boberg KM, Bergquist A, Mitchell S, et al. Cholangiocarcinoma in primary sclerosing cholangitis: risk factors and clinical presentation. Scand J Gastroenterol 2002; 37:1205-1211.
14. Stieber AL, Marino IR, Iwatsuki S, et al. Cholangiocarcinoma in sclerosing cholangitis: the role of liver transplantation. Int Surg 1989; 74:1-3.
15. Zein CO, Lindor KD, Angulo P. Prevalence and predictors of esophageal varices in patients with primary sclerosing cholangitis. Hepatology 2004; 39:204-210.
16. Wiesner RH, La Russo NF, Dozois RR, et al. Peristomal varices after proctocolectomy in patients with primary sclerosing cholangitis. Gastroenterology 1986; 90:316-322.
17. Gow PJ, Chapman RW. Liver transplantation for primary sclerosing cholangitis. Liver 2000; 20:97-103.
18. Brandsaeter B, Isoniemi H, Broome U, et al. Liver transplantation for primary sclerosing cholangitis: predictors and consequences of hepatobiliary malignancy. J Hepatol 2004; 40:815-822.
19. Graziadei IW. Recurrence of primary sclerosing cholangitis after liver transplantation. Liver Transpl 2002; 8:575-581.
20. Broome U, Lofberg R, Veress B, et al. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. Hepatology 1995; 22:1404-1408.
21. Wolf JM, Rybicki L, Ba L. Ursodeoxycholic acid is not chemoprotective for colorectal cancer in ulcerative coli-

tis patients with primary sclerosing cholangitis [abstract]. Gastroenterology 2001; 121:2276.
22. Pardi DS, Loftus EV Jr, Kremers WK, et al. Ursodeoxycholic acid as a chemoprotective agent in patients with ulcerative colitis and primary sclerosing cholangitis. Gastroenterology 2003; 124:889-893.
23. Danese S, Semerato S, Papa A, et al. Extraintestinal manifestations in inflammatory bowel disease. World J Gastroenterol 2005; 11:7227-7236.