Motion – Patients with primary sclerosing cholangitis should undergo early liver transplantation: Arguments for the motion

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Primary sclerosing cholangitis (PSC) is a condition of unknown etiology that causes progressive inflammation, fibrosis and obliteration of the intrahepatic and extrahepatic biliary tree. There is no medical cure, and ursodeoxycholic acid and other drugs have not been shown to affect the natural history of the disease. Endoscopic dilation is of value only in the relief of symptoms and complications related to dominant strictures. Cholangiocarcinoma occurs in a substantial minority of cases, especially those with ulcerative colitis and cirrhosis, and is often not clinically apparent before surgery. There are no good serologic tests for early cancers. Because this tumour has such a dismal prognosis, some authorities recommend that liver transplantation be undertaken before its development. This procedure is the only curative option for PSC, and excellent survival rates have been reported. There is evidence that early transplantation, before end stage liver disease or cholangiocarcinoma have developed, improves the survival and quality of life of patients with PSC. Because it is the only procedure of proven benefit, patients with PSC should be considered for liver transplantation early in the course of the disease.

Key Words: Liver transplant; Primary sclerosing cholangitis


Proposition – Les patients atteints de cholangite sclérosante primitive devraient subir une transplantation précoce du foie : arguments favorables

RÉSUMÉ : La cholangite sclérosante primitive (CSP) est une maladie d'étiologie inconnue qui provoque une inflammation évolutive, de la fibrose et l'oblitération de l’arbre biliaire intra- et extra-hépatique. Il n’existe pas de traitement médical, et l’acide ursodésoxycholique et d’autres médicaments sont sans effet sur le cours naturel de la maladie. La dilatation endoscopique ne permet que de soulager les symptômes et les complications liées aux sténoses importantes. Le cholangiocarcinome se rencontre chez une bonne minorité de patients, surtout chez ceux qui souffrent de rectocolite hémorragique ou de cirrhose, et souvent il est cliniquement muet avant l’intervention. Il n’existe pas de tests sérologiques fiables permettant de décéler les cancers précoces. En raison du sombre pronostic associé à la tumeur, certaines autorités recommandent de pratiquer une transplantation précoce du foie avant même son apparition. L’intervention constitue le seul traitement curatif de la CSP, et les taux de survie relevés sont excellents. Il est prouvé que la transplantation précoce, avant le stade ultime de l’hépatopathie ou l’apparition du cholangiocarcinome, améliore la survie et la qualité de vie des patients atteints de CSP. Étant donné qu’il s’agit de la seule intervention dont les avantages sont confirmés, les patients atteints de CSP devraient subir une transplantation précoce du foie.
Primary sclerosing cholangitis (PSC) is a chronic progressive liver disorder that is characterized by ongoing inflammation, fibrosis and obliteration of both intrahepatic and extrahepatic bile ducts. Diffuse strictures with short intervening segments of normal or increased diameter produce the characteristic beaded appearance at cholangiography. The pathogenesis of PSC is poorly understood, but available data suggest that immunological and other factors are involved (1). Most patients develop progressive diseases, including cirrhosis and portal hypertension.

Recognition of PSC as a distinct disease has been relatively recent. Until 1970, fewer than 100 patients with PSC had been reported, but the introduction of endoscopic retrograde cholangiography has increased our awareness of this disease. It is now acknowledged as one of the leading indications for liver transplantation (2).

While PSC responds poorly to medical therapy, the results of liver transplantation are excellent. Transplantation remains the only curative therapy and evidence is accumulating that, when undertaken early in the course of the disease, it may improve survival and the quality of life.

MEDICAL THERAPY
The evaluation of medical therapy of PSC has been limited by uncertainty about its cause and prognosis. It usually runs an indolent course, but PSC can be a rapidly progressive disease or can undergo spontaneous and unpredictable exacerbations and remissions. Therefore, even if a particular drug were to be effective, it would probably take years for this to be proven.

There is no effective pharmacological treatment for PSC, even though a variety of choleretic, immunosuppressive and antifibrotic agents have been tried. Despite early optimism for the use of ursodeoxycholic acid in small clinical studies, subsequent randomized controlled trials have revealed no benefit in slowing disease progression, delaying transplantation, or preventing complications or death (3-5). The following drugs have also been found to be ineffective in randomized trials: D-penicillamine (6), cyclosporine (7), methotrexate (8) and colchicine (9). Tacrolimus (FK 506) (10), nicotine (11) and pentoxifylline (12) have also yielded disappointing results in less rigorously-conducted studies.

ENDOSCOPIC THERAPY
Dominant strictures of the extrahepatic bile duct occur in 7% to 20% of patients with PSC (13). These can be treated with endoscopic balloon dilation or biliary stenting (14,15). Endoscopic dilation has been associated with a reduction in the frequency of episodes of cholangitis, improvements in biochemical tests and improvements in the cholangiographic appearance of the biliary tree. Its efficacy has not been demonstrated in randomized controlled trials, however, and it is not certain that it affects the natural history of the disease. Thus, endoscopic therapy has a limited role in PSC, and should be confined to the treatment of patients whose symptoms are due to a dominant extrahepatic stricture. In some patients, it can forestall liver transplantation, but the transplantation should not be delayed once manifestations of liver failure appear.

CHOLANGIOCARCINOMA
Cholangiocarcinoma reportedly occurs in 6% to 30% of cases of PSC (16). The risk is especially high for patients with chronic ulcerative colitis and cirrhosis. Most tumours occur at or near the junction of the right and left hepatic ducts. Serologic tumour markers, such as carcinoembryonic antigen and carbohydrate antigen 19-9 are neither highly sensitive nor specific for early, potentially treatable cholangiocarcinomas (17). Biliary brush cytology is also relatively unhelpful. Often, an unsuspected cholangiocarcinoma is first detected during pathological examination of the resected liver after transplantation.

Treatment of clinically apparent cholangiocarcinoma by resection, chemotherapy or radiation therapy has been discouraging. Liver transplantation is also generally unsuccessful in such cases (18), and most centres regard cholangiocarcinoma as a relative contraindication. Some experts have urged that liver transplantation be performed before this tumour develops.

RESULTS OF LIVER TRANSPLANTATION
For patients with advanced PSC, liver transplantation is the only effective therapeutic option. Indications for liver transplantation include bleeding from varices or portal gastropathy, intractable ascites with or without spontaneous bacterial peritonitis, recurrent episodes of bacterial cholangitis, progressive muscle wasting and hepatic encephalopathy. A number of transplant centres now report excellent long term survival, including one institution with a four-year survival rate of 88% for patients with PSC (19,20).

Narrowing can occur in the transplanted bile ducts in a pattern that resembles that of the underlying PSC. Possible causes of these strictures include ischemia, chronic rejection and infectious cholangitis related to the Roux-en-Y biliary anastomosis and immunosuppression, but they occur more frequently than average in patients with PSC. It thus appears that PSC can recur after transplantation, although its incidence is unclear. One centre suggested that PSC recurs in up to 20% of cases (20), while others reported lower rates (21).

SELECTION AND TIMING OF LIVER TRANSPLANTATION
The results of liver transplantation in PSC are excellent, and this is the best option for patients with end stage liver damage. There are several reasons for performing transplantation early in the course of disease. Studies have shown that patients with severe disease have decreased survival compared with those with milder disease at the time of transplantation (22). Early transplantation improves survival, decreases morbidity and reduces overall costs.

A number of important prognostic factors have been identified, including some that are specific to PSC (22). Generic predictors of an unfavourable response include...
admission into the intensive care unit or the use of life-support measures, age greater than 65 years, poor nutritional status and the requirement for dialysis before or after transplantation. Poor prognostic factors that are more specific to PSC include a high Mayo risk score, previous biliary tract surgery and the presence of cholangiocarcinoma. A previous history of biliary tract surgery is associated with a higher rate of postoperative complications, as well as decreased survival after transplantation. Cholangiocarcinoma is associated with a two-year survival rate of less than 20% (23).

In summary, PSC is a medically refractory condition that generally progresses to end stage liver disease and is curable with liver transplantation. Cholangiocarcinoma frequently complicates the disease and cannot be readily diagnosed in an early stage. Early transplantation has a beneficial impact on the long term prognosis, and should be undertaken before the development of cancer or end stage liver disease.

Patients with PSC should undergo early liver transplantation

REFERENCES