LIVER, BILIARY, AND PANCREAS

Improving biliary-enteric drainage in primary sclerosing cholangitis: experience with endoscopic methods

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Abstract

Six jaundiced patients with primary sclerosing cholangitis and a dominant biliary stricture were managed by endoscopic placement of endoprotheses. Five showed considerable improvement within weeks of stenting: their serum bilirubin concentration fell from mean (range) 266 $\mu\text{mol/l}$ (63–681) to 65 $\mu\text{mol/l}$ (10–280) after one month. One patient required a liver transplant at five months because of continued deterioration in hepatic function. Follow up of 12–49 months in the remaining five patients shows sustained biochemical improvement, with repeat cholangiograms indicating doubling of the minimum calibre of the extrahepatic bile duct in four patients and considerable shortening of stricture length in three. Three patients developed sepsis at the time of the initial endoprosthesis insertion: surgical drainage was necessary in one. Endoscopic methods of improving biliary-enteric drainage in jaundiced patients with primary sclerosing cholangitis may be preferable to surgical and percutaneous methods, which may complicate subsequent liver transplantation.

Primary sclerosing cholangitis is a progressive and often fatal disease of the liver, characterised by chronic inflammatory destruction of intrahepatic and extrahepatic bile ducts and associated with recurrent episodes of destructive bacterial cholangitis.^{1,2} Attempts at influencing the course of this condition using medical therapy have been disappointing,^{3–7} although preliminary results with ursodeoxycholic acid and methotrexate are promising.^{8,9} Similarly, attempts at changing the progressive nature of

the disease by nasobiliary drainage and lavage, with or without instillation of corticosteroids,^{10,11} or by surgical resection of dominant hilar strictures,¹² have not been effective.

Several investigators have shown improvement in clinical, radiological, and biochemical parameters after surgical or percutaneous placement of an endoprosthesis^{13,14} or balloon dilatation.^{15,16} Some of these procedures have a significant morbidity and others involve extensive surgery, which may not be desirable in the long term in these patients as it may jeopardize the success of future hepatic transplantation.^{17,18} We describe the clinical course in six severely symptomatic patients with primary sclerosing cholangitis in whom endoprotheses placed endoscopically led to an appreciable and sustained improvement in the clinical, biochemical, and radiological assessment of their disease.

Patients and methods

Between January 1986 and January 1990, 38 new patients were referred to our unit with confirmed or suspected primary sclerosing cholangitis. The extent of disease was determined by endoscopic retrograde cholangiography (ERC) and liver biopsy. Six patients (16%) were considered suitable for management by endoprosthesis insertion. This decision was based on the presence of strictures that severely reduced (by 50%) the bile duct calibre at the hilum or in the extrahepatic bile ducts, with good intrahepatic filling seen on ERC together with recent onset of deep jaundice (within six months). There were three men and three women, aged 25–54 years. When considered for endoprosthesis insertion, the mean serum bilirubin concentration was 266 $\mu\text{mol/l}$ (range 63–681). Two of the six patients had ulcerative colitis and four had established cirrhosis. All had symptoms of pruritus or fatigue, two had recurrent bacterial cholangitis (at least two episodes in the preceding 12 months), and five of the patients had been referred specifically for consideration of liver transplantation (Table). No patient received specific therapy – for example ursodeoxycholic acid – before or after stenting.

The endoscopic procedures were carried out with antibiotic prophylaxis; intravenous amoxycillin (500 mg) and either ceftazidime (2 g) or gentamicin (80 mg) were given immediately

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Clinical details of primary sclerosing cholangitis (PSC) patients at referral

	Patient no					
	1	2	3	4	5	6
Age (yrs)/sex	30F	54M	49M	25F	40F	31M
Duration of PSC (mths)	36	12	1	5	36	96
Duration of jaundice (mths)	6	3	1	5	3	3
Duration of ulcerative colitis (yrs)	0.5	0	21	0	0	0
Bilirubin ($\mu\text{mol/l}$)	124	63	681	147	476	104
Albumin (g/l)	36	40	36	34	35	34
Alkaline phosphatase (iu/l)	1864	631	386	915	1865	363
Aspartate transaminase (iu/l)	215	53	49	65	102	80
Histology grade	II	IV	I	IV	III	IV

Figure 1: Bilirubin and alkaline phosphatase values immediately before stenting and serial measurements afterwards. The most dramatic changes were seen within the first week. Each patient is identified by a number as in the Table.

before and eight hours afterwards. Patients were sedated with intravenous diazepam and pethidine, with the addition of hyoscine n-butyl hydrochloride to reduce gut motility. Diagnostic ERCs were carried out with a Pentax duodenoscope (SD32H). Cannulation of the common bile duct was successful at first attempt in all cases. All six patients had both intrahepatic and extrahepatic radiological features of primary sclerosing cholangitis. In five there were long strictures (>1 cm) in the common bile duct, and in two strictures affected the common hepatic and main hepatic ducts in addition to the common bile duct. Five patients also had moderately severe intrahepatic disease. Dominant strictures were initially dilated endoscopically using serial angioplasty inflation balloons up to a maximum of 8 mm (Surgimed, Meadox) through an Olympus TJF10 duodenoscope. Endoprostheses

(straight, 10 FG, tailored length, Wilson-Cook) were positioned across strictures using standard guide wire techniques.

Results

Endoprostheses were placed endoscopically in five of the patients without resort to sphincterotomy or a combined percutaneous approach. In one patient a sphincterotomy was necessary to facilitate passage of the endoprosthesis. Satisfactory drainage was achieved at first insertion in five patients but the sixth required repositioning of the stent five days after the first attempt. Pruritus was completely relieved within seven days in five patients. Serum bilirubin and alkaline phosphatase values fell rapidly from mean (range) values of 266 µmol/l (63–681) and 1004 iu/l (363–1965) respectively before stenting to 68 µmol/l (30–128) and 600 iu/l (208–1367) after one week, and in three patients normal values were attained (Fig 1). One patient underwent transplantation five months after treatment because of clinical hepatic decompensation. The other five remain well and asymptomatic after a mean (range) of 25 months (12–49) follow up, apart from a variceal haemorrhage in one patient. Follow up ERCs in these five patients show measurable radiological improvement in four (Fig 2). The minimum calibre of extrahepatic ducts in these patients has at least doubled (Fig 3) and the length of the dominant extrahepatic stricture has been reduced appreciably in three.

Endoprostheses were removed without replacement in four patients six to 13 months after initial insertion, with sustained clinical improvement. In one other patient a stent removed at four months had to be replaced 10 months later because of a rising bilirubin concentration: there was a second prompt response in the bilirubin concentration after replacement.

Despite the use of prophylactic broad spectrum antibiotics, two patients developed bacteraemia after insertion of endoprosthesis but this resolved on continued treatment. Distension of the gall bladder developed in two patients during the first week after endoprosthesis insertion and required percutaneous drainage in one and cholecystectomy in the other. There were no complications related to follow up ERC or stent replacement.

Discussion

It is likely that in primary sclerosing cholangitis considerable secondary liver damage occurs as a result of bile acid stasis and recurrent bacterial infection that lead to destructive cholangitis and secondary biliary cirrhosis. Methods of improving biliary drainage in this condition are aimed at ameliorating the effects of these pathological mechanisms. According to one survival model for this condition,¹⁹ five of our patients had a 12 month survival probability of less than 50% at the time of referral and warranted consideration for transplantation. Five improved considerably after insertion of the endoprosthesis and remain well 12–49 months later.

Several reports attest to the desirability of improving biliary drainage in primary sclerosing

Figure 2: Radiological appearances before (A) and after (B) stenting in patients 1, 2, and 3. The radiograms taken after stenting (B) are from the review endoscopic retrograde cholangiograms taken at least three months after removal of stents.

cholangitis in an attempt to change the natural history of the disorder. Choledochotomy with tube insertion and percutaneous drainage was superseded by a more aggressive surgical approach with the establishment of a choledochoenteric anastomosis with or without endoprosthesis.^{20 21} Cameron *et al*^{13 22} extended this

approach to include long term bilateral trans-hepatic Silastic catheters after excision of the hepatic duct bifurcation and bilateral hepatico-jejunostomy. The catheters were irrigated antegradely on a daily basis and by this means 26 of 31 patients showed sustained improvement after a three and a half year period. Russel *et al*²³

Figure 3: Radiological changes in extrahepatic bile duct calibre minima before and after stenting. Measurements were taken at review endoscopic retrograde cholangiography, which in four patients was at least three months after removal of stents. Each patient is identified by number as in the Table. No follow up measurements were available on the transplanted patient (No 5).

reported improvement in 10 of 15 patients with primary sclerosing cholangitis in whom percutaneous retrograde biliary dilatation was performed through a surgically created jejunal stoma access route. Krige *et al*²⁴ modified this approach by using a transhepatic U tube stent and reported improvement in six patients. In a series of 18 patients, Thompson *et al*¹² found that surgical drainage improves only patients with predominant extrahepatic primary sclerosing cholangitis. A short duration of preceding deep jaundice, as in the present patients, may also be important in determining the response to drainage.¹⁵

Percutaneous methods for hepatostomy drainage or dilatation have evolved in an attempt to avoid extensive biliary surgery. This technique may involve considerable time and resources, however, as detailed by Skolkin *et al*,¹⁶ who reported that percutaneous balloon cholangioplasty of intra- and extrahepatic ducts in 15 patients with primary sclerosing cholangitis required an average of 3.7 sessions and a mean (range) of 8.9 hours (4–18). In addition, it is associated with bacteraemia and intrapleural or intrabiliary haemorrhage in a significant proportion of patients.^{14,15}

Huibregtse and Tytgat²⁵ first described the management of primary sclerosing cholangitis strictures by endoscopic stenting after a sphincterotomy and have since described sustained improvement in 13 of 16 patients treated in this way.²⁶ Siegal and Guelrud²⁷ performed endo-

scopic balloon dilatation for strictures in two patients with primary sclerosing cholangitis, and Johnson *et al*²⁸ performed sphincterotomy in 10, subsequently dilating eight and stenting three. In Johnson's series, patients' liver biochemistry improved and the number of admissions to hospital for cholangitis was reduced over a two year follow up period, but one patient developed peritonitis as a result of sphincterotomy. We chose to avoid a sphincterotomy whenever feasible because of the long term risks of bacterial colonisation.²⁹ Three of our patients (50%) had septic complications, in two attributable to distension of the gall bladder at cholangiography with subsequent obstruction to emptying by the endoprosthesis. This is a complication that can be difficult to avoid in primary sclerosing cholangitis because of the extensive strictures and the relatively high filling pressures required to obtain a cholangiogram.

To date, there is insufficient experience to determine how long stents should be left in place. Some advocate leaving a percutaneous endoprosthesis in place for 12–16 months^{13,21} but others have reported such poor tolerance that the mean duration was <6 months.¹⁶ Huibregtse²⁶ removed the endoprosthesis permanently in eight of 16 patients without detectable deterioration at follow up. In four of our patients the endoprostheses have been removed and the patients remain well with continued improvement in the radiological assessment of disease. In one other patient the stricture recurred after removal of the endoprosthesis at four months. This patient's clinical condition deteriorated subsequently but the deterioration was reversed with further endoprosthesis insertion. That dramatic radiological improvement can be achieved even with short term stenting (see Fig 2), confirms a previous report of long term clinical outcome after short term stenting in patients with primary sclerosing cholangitis.³⁰ Similar beneficial effects have been reported in some series in which balloon dilatation was used alone.^{14–16,28} In none of these series were the patients as severely ill as in the present one, and in our experience balloon dilatation alone does not lead to long lasting remission in jaundiced patients with primary sclerosing cholangitis. Frequent follow up with a view to restenting is important as strictures recur in up to 50% of patients.^{14,15} An advantage of the endoscopic method is that lesions can easily be redilated or restented if necessary without the risks attendant on repeated surgery or transhepatic puncture.

The possible effect of endoprosthesis drainage upon disease progression is of some interest. The radiological extent of extrahepatic disease is associated with a poorer prognosis in primary sclerosing cholangitis.³¹ Reducing bilirubin and cholestasis, and perhaps prevention of cirrhosis, should change the natural history of the condition in individual patients according to the clinical models currently being proposed.^{32,33} Thus, according to the Mayo Clinic prognostic model, stenting improved the risk categories of our patients from high to moderate risk (two patients) and moderate to low risk (four patients). Nonetheless, it seems likely that methods used to improve biliary-enteric drain-

age are ultimately palliative in this condition and that most patients with primary sclerosing cholangitis will eventually require liver transplantation. With this in mind, endoscopic placement of endoprosthesis seems to be the drainage procedure of choice as it may avoid the disadvantages of surgical or percutaneous methods. A coordinated multicentre prospective study is required to assess the best means of biliary intervention in these patients and to determine whether broader criteria for such intervention are justified.

- 1 Chapman RWG, Arbough BAM, Rhodes J, *et al.* Primary sclerosing cholangitis: a review of its clinical features, cholangiography and hepatic histology. *Gut* 1980; 21: 870-7.
- 2 La Russo NF, Wiesner RH, Ludwig J, MacCarty RL. Primary sclerosing cholangitis. *New Engl J Med* 1984; 310: 899-903.
- 3 Tinckler JS. Primary sclerosing cholangitis. *Postgrad Med J* 1971; 47: 666-70.
- 4 Burgert SL, Brown BP, Kirkpatrick RB, LeBrecque DR. Positive corticosteroid response in early primary sclerosing cholangitis [Abstract]. *Gastroenterology* 1984; 86: 1037.
- 5 Leiser A, Kadish U. Case report: beneficial effect of colchicine in a case of sclerosing cholangitis. *Am J Med Sci* 1986; 291: 416-8.
- 6 La Russo NF, Wiesner RH, Ludwig J, MacCarty RL, Beever SJ, Zinsmeister AR. Prospective trial of penicillamine in primary sclerosing cholangitis. *Gastroenterology* 1988; 95: 1036-42.
- 7 Lindor KD, La Russo NF, Wiesner RH. Prednisone and colchicine are not of benefit after two years in patients with primary sclerosing cholangitis [Abstract]. *Hepatology* 1989; 10: 638.
- 8 Kaplan MM, Arora S, Pincus SH. Primary sclerosing cholangitis and low-dose oral pulse methotrexate therapy. *Ann Intern Med* 1987; 106: 231-5.
- 9 Stiehl A, Raedsch G, Thielmann L. Treatment of primary sclerosing cholangitis with ursodeoxycholic acid: first results of a controlled study [Abstract]. *Hepatology* 1989; 10: 612.
- 10 Grijm R, Huibregtse K, Bartelsman J, Mathus Vliegen EMH, Dekker W, Tytgat GN. Therapeutic investigations in primary sclerosing cholangitis. *Dig Dis Sci* 1986; 31: 792-8.
- 11 Allison MC, Burroughs AK, Nune P, Summerfield JA. Biliary lavage with corticosteroids in primary sclerosing cholangitis: a clinical, cholangiographic and bacteriologic study. *J Hepatol* 1986; 3: 118-22.
- 12 Thompson JS, Wood RP, Burnett DA, Shaw BW, Rikkers LF. The role of non-transplant procedures for sclerosing cholangitis. *Am J Surg* 1988; 156: 506-8.
- 13 Cameron JL, Pitt HA, Zinner MJ, *et al.* Resection of hepatic duct bifurcation and transhepaticstenting for sclerosing cholangitis. *Ann Surg* 1988; 207: 614-22.
- 14 Mueller PR, vanSonnenberg E, Ferruci JT, *et al.* Biliary stricture dilatation: multicentre review of clinical management in 73 patients. *Radiology* 1986; 160: 17-22.
- 15 May GR, Bender CE, LaRusso NF, Wiesner RH. Non-operative dilatation of dominant strictures in primary sclerosing cholangitis. *Am J Radiol* 1985; 145: 1061-4.
- 16 Skolkin MD, Alspaugh JP, Casarella WJ, Chuang VP, Galambos JT. Sclerosing cholangitis: palliation with percutaneous cholangioplasty. *Radiology* 1989; 170: 199-206.
- 17 Marsh JW, Iwatsuki S, Makowka L, *et al.* Orthotopic liver transplantation for primary sclerosing cholangitis. *Ann Surg* 1988; 207: 21-5.
- 18 Roberts MS, Pinson CW, Karlson C, *et al.* Predictors of intraoperative death and long-term survival in liver transplantation: a multistage analysis. *Transplant Proc* 1989; 21: 2439-42.
- 19 Lebovics E, Palmer M, Woo J, Schaffner FS. Outcome of primary sclerosing cholangitis: analysis of long-term observation for 38 patients. *Arch Intern Med* 1987; 147: 729-31.
- 20 Pitt HA, Thompson HH, Tompkins RK, Longmire WP. Primary sclerosing cholangitis: results of an aggressive surgical approach. *Ann Surg* 1982; 196: 259-68.
- 21 Wood RAB, Cuschieri A. Is sclerosing cholangitis complicating ulcerative colitis a reversible condition. *Lancet* 1980; ii: 716-8.
- 22 Cameron JL, Gayler BW, Herlong HF, Maddrey WC. Sclerosing cholangitis: biliary reconstruction with Silastic transhepatic stents. *Surgery* 1983; 94: 324-30.
- 23 Russel E, Yrizarry JM, Huber JS, *et al.* Percutaneous transjejunal biliary dilatation: alternative management for benign strictures. *Radiology* 1986; 159: 209-14.
- 24 Krige JEJ, Terblanche J, Harries-Jones EP, Bornman PC. Primary sclerosing cholangitis: biliary drainage and dilatation. *Br J Surg* 1987; 74: 54-7.
- 25 Huibregtse K, Tytgat GN. Palliative treatment of obstructive jaundice by transpapillary introduction of large bore bile duct endoprosthesis. *Gut* 1982; 23: 371-5.
- 26 Huibregtse K. Therapeutic investigations in primary sclerosing cholangitis. In: *Endoscopic biliary and pancreatic drainage*. Stuttgart: George Thieme Verlag, 1988: 78-85.
- 27 Siegal JH, Guelrud M. Endoscopic cholangiopancreatography: hydrostatic balloon dilatation in the bile duct and pancreas. *Gastrointest Endosc* 1983; 29: 99-103.
- 28 Johnson GK, Geenan JE, Venu RP, Hogan WJ. Endoscopic treatment of biliary duct strictures in sclerosing cholangitis: follow-up assessment of a new therapeutic approach. *Gastrointest Endosc* 1987; 33: 9-12.
- 29 Escourrou J, Cordova JA, Lazorthes F, Frexinos J, Ribet A. Early and late complications after endoscopic sphincterotomy for biliary lithiasis with and without the gall-bladder 'in-situ'. *Gut* 1984; 25: 598-602.
- 30 Hamilton I, Soutar JS, Bouchier IA, Cuschieri A. Short-term biliary dilatation and stenting in primary sclerosing cholangitis. *J Clin Gastroenterol* 1987; 9: 70-5.
- 31 Sherlock S. Primary sclerosing cholangitis. In: *Diseases of the liver and biliary system*. 8th ed. Oxford: Blackwell Scientific, 1988: 289-300.
- 32 Helzberg JH, Petersen JM, Boyer JL. Improved survival with primary sclerosing cholangitis: a review of clinicopathologic features and comparison of symptomatic and asymptomatic patients. *Gastroenterology* 1987; 92: 1869-75.
- 33 Wiesner RH, Grambsch PM, Dickson DR, *et al.* Primary sclerosing cholangitis: natural history, prognostic features and survival analysis. *Hepatology* 1989; 10: 430-6.