

# **Biodegradable STents in Primary Sclerosing Cholangitis -BSTPSC**

## **Pilot Study protocol**

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## **1. Background**

Primary sclerosing cholangitis (PSC) is a rare cholestatic disorder with a prevalence of 16.2 per 100,000 population; it is characterised by progressive inflammation and destruction of the intra and/or extrahepatic bile ducts culminating in progressive fibrosis and cirrhosis(1-3). It most commonly affects men between the ages of 30- 40 and occurs in the presence of inflammatory bowel disease. It can be detected as part of patient evaluation in IBD or can present with fatigue, abdominal pain, pruritus or jaundice (4). The aetiology of PSC is unclear but may involve cholangiocyte injury resulting from an abnormal immune response to environmental exposure in genetically susceptible individuals (3, 4). Patients with PSC are at risk of both benign and malignant biliary obstruction. Worsening cholangitis with fever, pain and jaundice should prompt further investigation. Poor prognostic factors in PSC include extensive biliary strictures, recurrent cholangitis, evidence of liver synthetic dysfunction and dominant strictures (4). There is no effective medical therapy that has been shown to alter the natural history of the disease. Treatment revolves around managing symptoms and complications as they arise. Trials into medical therapy are currently focused on cholestatic and fibrotic targets (4). Liver transplantation is currently the only therapeutic approach for eligible patients with end-stage disease, but disease recurrence in the graft can be as high as 25% (3).

Clinically significant biliary strictures occur in 45- 65% of patients with PSC (5, 6). Strictures are classified as high grade on MRCP with 75% reduction of duct diameter in the common bile duct or hepatic ducts(6). Patients with new or worsening bile duct stricture with or without signs/symptoms suspicious of malignancy should undergo ERC (4, 5). Symptoms include cholangitis, progressive jaundice and pruritus with evidence of progressive bile

duct dilatation on imaging. Patients who develop high grade, clinically relevant strictures have an increased risk of cholangiocarcinoma, which can occur in up to 26% of patients with significantly reduced overall survival compared to those without high grade strictures (7). High grade strictures should be interrogated via ERC to investigate for the presence of a malignant stricture with tissue obtained via brushings for cytology and consideration of cholangioscopy and biopsy, which has higher sensitivity with comparable specificity (6, 8, 9).

In patients undergoing stenting in PSC, plastic stents are the primary intervention. These small-diameter stents can develop biofilms and occlude over time, possibly leading to cholangitis (10). Biodegradable stents are increasingly being used in a variety of indications (11, 12). They are a novel alternative that may confer benefit in the reduction of treatment-related adverse events by removing the necessity of repeat procedures for stent removal. They are made of polydioxanone (a synthetic biodegradable polymer). These stents have been clinically effective and safe in patients with symptomatic biliary obstruction (12, 13). They hydrolyse with variable degradation times. Similar to plastic stents, they have an introducer that allows placement over the target area, and positioning can be visualised fluoroscopically. The Archimedes stent is a commercially available biodegradable stent produced by AMG International (14). Clinical utilisation of these stents demonstrating excellent safety and efficacy are now emerging (12, 13).

In patients with PSC, endoscopic therapy of strictures aims to improve cholestasis by relieving the biliary obstruction via endoscopic biliary dilatation with consideration of plastic stents in strictures refractory to dilatation due to the risk of pancreatitis and cholangitis (15-17). Short term stents have been shown to have similar recurrence-free

rates compared to dilatation in a randomised control trial; however, this was terminated after interim analysis due to higher rates of serious adverse events in the stent group (15). The long term benefits are unclear; however, it may lead to improved survival compared to predicted survival (18). In this group of patients with limited treatment options, biodegradable stents may provide an attractive additional treatment modality in the management of high grade strictures.

## **2. AIMS**

### **Research hypothesis**

The use of biodegradable stents leads to remodelling of high grade strictures in patients with PSC with fewer interventions in comparison to balloon dilation alone with a comparable risk profile to current therapy.

### **Primary endpoint**

Technical success and safety of biodegradable stent placement at ERC

### **Secondary endpoints**

- Cumulative recurrence -free rate of primary high grade strictures within 12 months
- Change in symptoms as assessed by the Amsterdam cholestatic complaints score (ACCS)(19)
- Clinical success is defined by improvement in liver function tests (LFT) by 20% at week 2 and week 12.
- Improvement in quality of life as assessed by the Short form-36 (SF-36).
- Mortality, morbidity, local complications, stricture recurrence, decompensation of liver disease, liver transplantation over 12 months.

### **3. Methods**

#### **Study design**

Single centre, open-label, single group pilot study with a follow up of 12 months.

#### **Sample size**

A prospective study (15) demonstrated a re-intervention free rate of 55% at 12 months for balloon dilatation. Assuming the re-intervention free survival rate at 12 months would be 55% for balloon dilatation (Group B) vs 15% for short term stenting with a biodegradable stent (Group A) yielded a sample size of  $n = 21$  per group. Allowing for a drop out rate of 15%, rendered a total sample size of 50 to attain a power of 80% and a 2-sided alpha level of 0.05. An interim analysis is planned when 50% of the intended total number of study subjects had passed their 3-month visit. We aim to enroll 21 prospective patients into Group A and use a historical cohort for Group B (undergone balloon dilatation in the last 5 years at King's College Hospital). A sample size of 21 was calculated (confidence 0.90, probability 0.1).

#### **Participants**

Eligible patients with a diagnosis of PSC according to the European association for study of liver 2009 criteria, ascertained with MRCP, ERC, percutaneous transhepatic cholangiography and/or liver biopsy were between 18-75 years of age and fulfilled at least 1 of the following 5 criteria sets: (1) serum bilirubin  $> 3$  times the upper limit of normal (ULN); (2) progression of right upper quadrant pain (RUQP), pruritus, fatigue and/or fever attributed to acute bacterial cholangitis by at least 1 grade according to the Amsterdam Cholestatic Complaints score (ACCS) within the last month, together with a 50% increase of total bilirubin and/or ALP within

the last 4 months and absolute value > 1.2 times the ULN; (3) increase of 20% or more of total bilirubin and/or ALP within the last 4 months and absolute value > 1.2 times the ULN, together with a documented dominant appearing stricture on MRCP or ERC < 4 months before screening; (4) progression of RUQP, pruritus, fatigue and/or fever attributed to bacterial cholangitis by at least 1 grade within the last month, together with total bilirubin and/or ALP > 1.2 times the ULN and a documented stricture on recent MRCP or ERC < 4 months before screening; (5) summed cholestatic complaints score of  $\geq 3$ , or pruritus  $\geq 2$ , or RUQP  $\geq 2$  at screening, together with total bilirubin and/or ALP > 1.2 times the ULN and a documented dominant stricture on recent MRCP or ERC < 4 months before screening. A dominant stricture was defined as any stricture arising in the extrahepatic or left/right main ducts that was deemed functionally relevant by the treating endoscopist/radiologist.

All participants will provide written consent. Eligible patients will be:

- Patients with PSC without evidence of decompensation of chronic liver disease (ascites, hepatic encephalopathy).
- Evidence of a high grade stricture (>75% narrowing) on Magnetic resonance cholangiopancreatography (MRCP) with bile duct dilatation with no evidence of decompensation of liver disease and no other possible causes of elevated liver tests.
- Participants will be aged 18 years or older.
- The decision to proceed to an ERC will be in the Liver Xray/autoimmune MDT as per standard of care (SOC).

A high grade stricture is defined as a biliary stricture on MRCP with > 75% reduction of the duct diameter in the common bile duct or hepatic ducts. A relevant stricture is a high-grade biliary stricture on imaging in the common bile duct or hepatic ducts with signs or symptoms of obstructive cholestasis (rise in liver bloods tests, itch) and/or bacterial cholangitis.

All ERC and stent insertion attempts are to be carried out by an experienced operator. All procedures are to be carried out under general anaesthetic as per unit protocol. Medium degradation stents only to be used. All patients will receive intravenous Tazocin 4.5g pre/peri-procedure followed by 2 doses after. In the event of a penicillin allergy, intravenous Ciprofloxacin 500mg will be given with 2 further doses post procedure. All patients will be considered for pre/peri-procedural NSAID.

Patient information and informed consent will be obtained at ERC preassessment alongside physical examination and liver biochemistry. Insertion of the stent via ERC with endoscopist questionnaire on ease of placement, visibility on fluoroscopy, the maximum diameter of the stricture, whether dilatation was used and any procedure-related complications. Patient follow up on day one post insertion with questionnaires with a structured interview to assess for procedure-related symptoms and post-insertion AE. Liver function tests and telephone consultation on week 2 (up to 14 days post procedure) to assess for stent degradation, clinical response to therapy, complications and morbidity. MRCP at week 52 to assess for stricture remodelling with improvement in liver biochemistry. Patients will be closely monitored with access to the clinical team involved in the study. The pilot study will be carried out over 24 months.

**Exclusion criteria**

- Prior stenting or balloon dilatation within the previous 4 months
- Signs of bacterial cholangitis as defined by definite cholangitis according to the criteria in Supp Table 2 (Poinesen et al, Gastro 2015)
- Change of UDCA therapy within 4 weeks
- Inability to give informed consent
- Biliary cirrhosis with Child Pugh score  $\geq 8$
- Estimated transplant free survival < 2 years as calculated by Mayo score > 2
- Suspicion of cholangiocarcinoma, reflected by an imaging study suggestive of metastasis, MRCP with mass lesion with contrast enhancement, or rise in CA19.9 of > 63 U/ml in the previous 4 months together with an absolute value > 130 U/ml
- Signs of current malignancy other than basal cell carcinoma
- Life expectancy < 24 months
- Women pregnant at the time of screening
- HIV or acute or chronic hepatitis B or hepatitis C or substance (drug or alcohol) misuse within the previous 2 years.

**Interventions**

Eligible patients will undergo ERCP after informed consent. Periprocedural antibiotic prophylaxis will consist of intravenous piperacillin-tazobactam 4.5g or intravenous ciprofloxacin 500mg, and a subsequent dose 6 or 12 hours after.

Patients will be considered for the study only when, in the absence of purelant bile and fever > 38.5°C, 1 or more dominant stricture(s) of the common bile duct, the common hepatic duct and/or main left or right hepatic duct are encountered and deemed amenable to both balloon dilatation or stenting by the endoscopist. Before any intervention where possible, brush cytology will be obtained of any suspicious sominant stricture. If brush cytology demonstrates cholangiocarcinoma or high-grade dysplasia, that patient will be withdrawn from the study. Sphincterotomy will be performed at the discretion of the endoscopist.

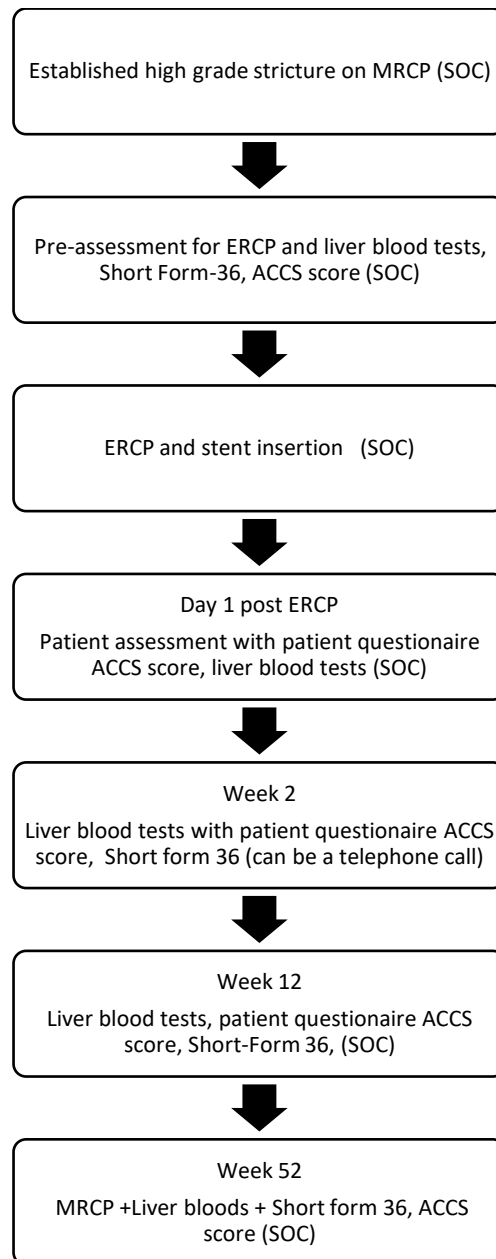
### **Stenting**

A 6Fr Archimedes (medium degradation) stent will be used for for strictures at the biliary hilum with consideration of bilateral stents if possible. 8Fr or 10Fr Archimedes (fast degradation) stents will be considered for dominant strictures in the common bile duct. Balloon dilatation (4mm or 6mm diameter) to facilitate stent placement will be allowed. If stent placement proved impossible after 2 ERCPs, then this will be classified as a failure. After the procedure, patients will be kept overnight for observation and intravenous antibiotics.

### **Ethical Consideration**

This study will be the first to analyse the feasibility of biodegradable stents in inflammatory liver pathology. The research protocol will be submitted to the Research ethics committee for approval. The study is to be conducted to ICH GCP standards.

#### 4. Study flow chart



MRCP, magnetic resonant cholangio-pancreatography; SOC, standard of care; ASSC, Amsterdam cholestatic complaint score; AXR, abdominal x ray.

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