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No Superiority of Stents vs Balloon Dilatation for Dominant Strictures in Patients With Primary Sclerosing Cholangitis

Cyriel Y. Ponsioen,[1] Urban Arnelo,[2] Annika Bergquist,[2] Erik A. Rauws,[1] Vemund Paulsen,[3] Paolo Cantú,[4] Ilaria Parzanese,[4] Elisabeth M. De Vries,[1] Kim N. Van Munster,[1] Karouk Said,[2] Olivier Chazouillères,[5] Benoit Desaint,[5] Astrid Kemgang,[5] Martti Färkkilä,[6] Schalk Van der Merwe,[7] Werner Van Steenbergen,[7] Hanns-Ulrich Marschall,[8] Per-Ove Stotzer,[8] Douglas Thorburn,[9] Stephen P. Pereira,[9] and Lars Aabakken[3]

[1]Department of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, the Netherlands; [2]Department of Gastroenterology & Hepatology, Karolinska University Hospital, Huddinge, Karolinska Institutet, Sweden; [3]Department of Gastroenterology & Hepatology, Rikshospitalet, Oslo, Norway; [4]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy; [5]Department of Hepatology, Hôpital Saint Antoine, Paris, France; [6]Department of Gastroenterology & Hepatology, Helsinki University Hospital, Helsinki, Finland; [7]Department of Gastroenterology & Hepatology, Universiteitsziekenhuis Leuven, Leuven, Belgium; [8]Department of Hepatology, Sahlgrenska University, Gothenburg, Sweden; and [9]Institute of Liver & Digestive Health, University College London and Sheila Sherlock Liver Centre, Royal Free Hospital, London, United Kingdom

BACKGROUND & AIMS: Dominant strictures occur in approximately 50% of patients with primary sclerosing cholangitis (PSC). Short-term stents have been reported to produce longer resolution of dominant strictures than single-balloon dilatation. We performed a prospective study to compare the efficacy and safety of balloon dilatation vs short-term stents in patients with non–end-stage PSC. **METHODS:** We performed an open-label trial of patients with PSC undergoing therapeutic endoscopic retrograde cholangiopancreatography (ERCP) at 9 tertiary-care centers in Europe, from July 2011 through April 2016. Patients found to have a dominant stricture during ERCP were randomly assigned to groups that underwent balloon dilatation (n = 31) or stent placement for a maximum of 2 weeks (n = 34); patients were followed for 24 months. The primary outcome was the cumulative recurrence-free patency of the primary dominant strictures. **RESULTS:** Study recruitment was terminated after a planned interim analysis because of futility and differences in treatment-related serious adverse events (SAEs) between groups. The cumulative recurrence-free rate did not differ significantly between groups (0.34 for the stent group and 0.30 for the balloon dilatation group at 24 months; $P > 1.0$). Most patients in both groups had reductions in symptoms at 3 months after the procedure. There were 17 treatment-related SAEs: post-ERCP pancreatitis in 9 patients and bacterial cholangitis in 4 patients. SAEs occurred in 15 patients in the stent group (45%) and in only 2 patients in the balloon dilatation group (6.7%) (odds ratio, 11.7; 95% confidence interval, 2.4–57.2; $P = .001$). **CONCLUSIONS:** In a multicenter randomized trial of patients with PSC and a dominant stricture, short-term stents were not superior to balloon dilatation and were associated with a significantly higher occurrence of treatment-related SAEs. Balloon dilatation should be the initial treatment of choice for dominant strictures in patients with PSC. This may be particularly relevant to patients with an intact papilla. ClinicalTrials.gov no. NCT01398917.

Keywords: Biliary; Drainage; Surgery; Temporary Stent.

Primary sclerosing cholangitis (PSC) is a chronic fibroinflammatory disease of the biliary tree of unknown origin. It is a progressive disease, which causes end-stage liver failure and is associated with an increased risk of cholangiocarcinoma. Transplant-free survival is estimated between 12 and 21 years.[1,2] Currently, therapy is limited to treatment of complications such as relieving biliary obstruction and orthotopic liver transplantation in case of end-stage liver disease.[3,4]

During the natural history of the disease, many patients experience symptoms such as pruritus, right upper quadrant pain (RUQP), fatigue, and/or bouts of fever and jaundice because of impeded biliary drainage. In approximately 60% of cases, dominant strictures (DS), which may be superimposed on diffuse ductal disease, are the principal cause of these complaints.[5] The incidence is estimated at 8%–10% annually.[6]

The 2015 guidelines from the American Society for Gastrointestinal Endoscopy (ASGE) on the role of endoscopic retrograde cholangiopancreatography (ERCP) state that patients with PSC and DS should undergo ERCP with biliary sampling to assess for presence of malignancy.[7] Moreover, benign strictures respond well to endoscopic therapy. Recommendations from a recent collaboration between the European Association for Study of the Liver and the European Society of Gastrointestinal Endoscopy to develop guidelines

Abbreviations used in this paper: **ACCS, Amsterdam Cholestatic Complaints Score; ALP, alkaline phosphatase; ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; DS, dominant stricture; DSMB, data safety monitoring board; ERCP, endoscopic retrograde cholangiopancreatography; PSC, primary sclerosing cholangitis; MRCP, magnetic resonance cholangiopancreaticography; PEP, post–endoscopic retrograde cholangiopancreatography pancreatitis; RUQP, right upper quadrant pain; SAE, serious adverse event; SF36, Short Form–36; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

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NEW FINDINGS

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LIMITATIONS

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IMPACT

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on endoscopy in PSC are in line with the ASGE statements.[8,9] The level of evidence reviewed in both guidelines is low, however, based only on retrospective series.

The best therapeutic approach to treat dominant strictures is not known. Both balloon dilatation and temporary stenting are used. From the largest retrospective series on repetitive balloon dilatation, one may infer that the recurrence-free rate at 2 years after a single session of endoscopic balloon dilatation is approximately 30%.[6]

Ponsioen et al. reported that short-term stenting with a mean duration of stent placement of 11 days is safe and effective, showing improvement of cholestatic symptoms and biochemistry in 83% of patients at 8 weeks and a re-intervention–free rate of 70% at 2 years.[5] We hypothesized that short-term stenting is superior to balloon dilatation at preventing recurrence of DS. Therefore, the aim of the present study was to compare short-term stenting vs balloon dilatation for the treatment of dominant strictures in patients with PSC with regard to cumulative recurrence-free patency, safety, and short-term improvement in cholestatic symptoms and biochemistry.

Methods

Study Design

We undertook a multicenter, open-label, randomized, 1:1 parallel group trial with a follow-up of 24 months. Eligible patients were randomized during ERCP when a DS was identified to either balloon dilatation or short-term stenting for a maximum of 2 weeks.

Participants

Eligible patients had a diagnosis of PSC according to the European Association for Study of the Liver 2009 criteria,[10] ascertained with magnetic resonance cholangiopancreaticography (MRCP), ERCP, PTC, and/or liver biopsy, were between 18 and 75 years of age, and fulfilled at least 1 of the following 5 criteria sets: (1) serum bilirubin level $>$ 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)[5] (Supplementary Table 1) within the last month, together with a 50% increase of total bilirubin and/or alkaline phosphatase (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 ERCP $<$ 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 dominant stricture on recent MRCP or ERCP $<$ 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 ERCP $<$ 4 months before screening. Criteria sets 4 and 5 were added to the eligibility criteria to increase recruitment after additional institutional review board approval in March 2013 and May 2015, respectively. All eligibility sets were designed to reflect clinical practice with regard to indication for endoscopic intervention and to allow for detection of relevant changes during follow-up. On imaging, 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.

Exclusion criteria were prior stenting or balloon dilatation within the previous 4 months; signs of bacterial cholangitis as defined by definite cholangitis according to the criteria in Supplementary Table 2[11]; change of ursodeoxycholic acid (UDCA) therapy within 4 weeks; inability to give written informed consent; biliary cirrhosis with Child-Pugh score $\geq$ 8; estimated transplant-free survival $<$ 2 years, as calculated by a 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; use of antibiotics in previous 4 weeks; 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.

Outcome

The primary endpoint was the cumulative recurrence-free rate of the primary DS(s) within 24 months in those patients who did not experience initial failure (Supplementary Figure 2). Ideally, assessment of recurrence of the treated DS(s) would require successive ERCPs at regular intervals during follow-up. Because this is not possible for obvious ethical reasons, a decision rule for repeated ERCP was determined based on either (1) recurrence of serum bilirubin level back to screening level if $>$ 3 times the ULN; (2) increase of ALP or bilirubin $\geq$ baseline level, together with increase in a cholestatic complaint $\geq$ 1