Biodegradable stents for the treatment of benign stenoses of the small and large intestines

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Introduction
Endoscopic therapy and stenting of refractory benign gastrointestinal stenoses remains challenging [1–3]. Stents made of biodegradable materials may be able to avoid the shortcomings of metallic and plastic stents (mucosal hyperplastic reaction, shorter patency, migration) and do not require subsequent removal [4–10]. Fry & Fleischer [11] and Goldin et al. [12] were the first to report the insertion of biodegradable stents made of poly-L-lactide for refractory benign esophageal stricture, and several similar case reports and small clinical studies with limited numbers of patients followed [13–20]. Parviainen et al. [21] piloted poly lactide biodegradable stents for pancreaticojejunal anastomoses in two patients. Petryl et al. [22] successfully introduced biodegradable stents percutaneously into intraperitoneal biliary strictures in two patients. Laukariinen et al. [23] tried biodegradable poly lactide stents for surgical intra-anastomotic placement in hepaticojejunal anastomosis. To the best of our knowledge, we were the first to report on the successful use of biodegradable stents in the small bowel [24]. The aim of this paper is to report on the methods of introduction and on the long-term follow-up of a series of patients with biodegradable stents for benign intestinal stenoses.

Case series
Patients
Between August 2008 and January 2010, 11 patients (8 men, 3 women; mean age 43, median age 41, range 32–58) with Crohn’s disease and significant gastrointestinal stenoses were entered into this prospective study. The stenoses were found in the large bowel in two patients, and the small intestine in one patient, with the remainder located at the sites of small–large-intestinal anastomoses following previous surgery. Other clinical details for the patients are given in Table 1. All patients provided written informed consent prior to the procedure.

Biodegradable stents
Biodegradable stents made of polydioxanone (SX-ELLA BD biodegradable stent; ELLA-CS, Hradec Kralove, Czech Republic) were used in all patients. These stents provide an extended period of dilation compared with conventional methods, with stent integrity and radial force maintained for 6–8 weeks after implantation. Stent degradation and fragmentation occurs 11–12 weeks after insertion; the speed of degradation being pH-dependent (faster at lower pH). The dual flared-end stent design reduces the risk of migration [25]. These biodegradable stents were originally designed and developed for esophageal stenoses, but we recently decided to try them for benign

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
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<tr>
<td>Stenoses of the small and large intestines</td>
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Table 1  Clinical details for the 11 patients with Crohn's disease and significant gastrointestinal stenoses who underwent biodegradable stent insertion.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex/age, years</th>
<th>Duration of Crohn's disease, years</th>
<th>Fistulas present</th>
<th>Significant stenosis</th>
<th>Extra-intestinal disease</th>
<th>Number of previous bowel resections</th>
<th>Drug treatment Before stent insertion</th>
<th>After stent insertion</th>
<th>Laboratory markers of activity</th>
<th>Clinical signs of disease activity</th>
<th>Signs of bowel obstruction</th>
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<tbody>
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<td>F/40</td>
<td>2</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>S-ASA, AZA</td>
<td>S-ASA, AZA</td>
<td>5</td>
<td>215</td>
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<tr>
<td>2</td>
<td>M/54</td>
<td>23</td>
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<td>Yes</td>
<td>Yes</td>
<td>2</td>
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<td>203</td>
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<td>F/32</td>
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<td>M/58</td>
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<td>152</td>
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<td>M/54</td>
<td>10</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
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<td>S-ASA, prednisone, AZA</td>
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<td>292</td>
<td>Yes</td>
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<td>6</td>
<td>M/35</td>
<td>10</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>0</td>
<td>S-ASA, ATNF</td>
<td>S-ASA, ATNF</td>
<td>6</td>
<td>144</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>M/36</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
<td>0</td>
<td>S-ASA, ATNF</td>
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<td>174</td>
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<td>8</td>
<td>M/44</td>
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<td>192</td>
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<td>9</td>
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<td>21</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>2</td>
<td>S-ASA, budesonide ATNF</td>
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<td>10</td>
<td>M/36</td>
<td>14</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>2</td>
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<td>0</td>
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<tr>
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<td>F/41</td>
<td>11</td>
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<td>Yes</td>
<td>No</td>
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<td>S-ASA, AZA, ATNF</td>
<td>S-ASA, AZA, ATNF</td>
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<td>356</td>
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</tbody>
</table>

CRP, C-reactive protein; M, male; F, female; S-ASA, mesalazine; AZA, azathioprine; MTX, methotrexate; ATNF, anti-TNF-α therapy.

* On spoon food and lactulose.
† After previous endoscopic dilation of multiple stenoses of the proximal jejunum.
‡ On total enteral nutrition.
intestinal stenoses. This project was approved by the Ethical Committee of our institution (Number 200906 S12P) and funded by a research grant.

Different sizes of stents and introducer systems were used for each patient according to the size of the stenosis, with outer stent diameters 18 – 25 mm (flared ends 23 – 27 mm) and lengths 40 – 80 mm. Three different designs were used (Fig. 1). Stents are fitted with radio-opaque markers at the midpoint and ends to enable precise stent positioning under fluoroscopic control. The standard delivery system for esophageal implantation, which can also be used for cases of distal (rectal) stenoses, consists of a shaft (outer diameter 28 Fr, length 75 cm) with a detachable olive (ELLA-CS; see Fig. 1). For more proximal stenoses, a special introduction system for stent insertion through a balloon overtube (TS-13140 or TS-13101; Fujinon, Saitama City, Japan) with outer diameter 8.5 mm has been developed. The stent must be loaded just before implantation.

Endoscopy

A double-balloon enteroscopy or colonoscopy system (Fujinon) was used for all patients. All procedures were performed via an anal approach and accomplished with the patients under conscious sedation (intravenous midazolam and pentazocine). A therapeutic enteroscope (EN 450T5; working channel 2.8 mm, outer diameter 9.4 mm, working length 200 cm) was inserted through an overtube (TS-13140; outer diameter 13.2 mm, length 145 cm), or a colonoscope (EC 450B5; working channel 2.8 mm, outer diameter 9.4 mm, working length 152 cm) was inserted through an overtube (TS-13101; outer diameter 13.2 mm, length 95 cm).

Intestinal stenoses were firstly dilated by through-the-scope balloon dilation (CRE Balloon; Boston Scientific, Natick, Massachusetts, USA), and the distal margins of the stenoses were marked with metallic clips and/or Lipiodol injection. The inflated balloon on the tip of the overtube secured the correct stable position during the procedure. Biodegradable stents were implanted over a stiff guide wire by means of a special introducer that was inserted into the enteroscope overtube after removal of the endoscope.

Stent placement was accomplished under fluoroscopic control. Kinking of the balloon overtube, mainly at the splenic flexure, during insertion of the introducer was the only technical problem. The enteroscope or colonoscope, which was used without a distal balloon to allow its smooth withdrawal through the overtube, was immediately reinserted via this overtube to check the correct positioning of the stent (Fig. 2 and 3, Video 1).

Results

Insertion of biodegradable stents was successful at the first attempt in all patients except one. No immediate complications of the procedure were recorded in any of the patients who underwent successful insertion. Any early, short-term, mild, dull abdominal pain experienced did not require painkillers, and stent insertion provided rapid clinical improvement and symptom relief.

Subsequent follow-up was for a mean of 16 months, median 17 months, range 12 – 29 months. Clinical and radiographic follow-up was performed 1 week after insertion and again 1 month later. No endoscopic follow-up was performed in patients who remained asymptomatic. Details of the procedures and the clinical outcomes are given in Table 2. Stent migration was recorded in three patients (in two of them waved stents, design B in Fig. 2, had been used). The two stents that migrated 2 days after their insertion did not show any mac-
roscopic signs of degradation. The stent that was observed fluoroscopically to have migrated from the ileo-transverse colon anastomosis to the sigmoid colon after 8 weeks had probably at least partly disintegrated, but the patient did not observe subsequent spontaneous passage of the stent. Except in the patients with stent migration (patients #5, #7, and #8) or stent shortening (patient #3), time to stent degradation was 4 months. “Full degradation” was assessed fluoroscopically as complete disappearance of the radio-opaque markers.

Discussion

Tight intestinal stenoses in Crohn’s disease and strictures that complicate other diseases may cause significant problems. Previously, they were treated by surgical resections (often extensive) or stricturoplasty; nowadays, they can be dilated endoscopically [26–28]. However, the duration of any benefit from this treatment may be limited, with repeated endoscopies and dilations necessary, and consequently possible risks of perforation. Biodegradable stents can be considered as a new therapeutic option [10]. These stents can be made of various synthetic polymers, such as polylactide or polyglycolide, or their co-polymer, such as polydioxanone. Their degradation is hydrolytic, with firstly the amorphous and then the crystalline structure broken down. The speed of biodegradation is dependent not only on their size and structure (crystallinity, porosity, and hydrophilic backbone, amongst others) but is also influenced by temperature, pH and the type of body tissue/fluid around them [29, 30].

Our experience so far with the use of biodegradable stents for stenoses of the small and large intestines is promising, although still in its early stages. Only a limited number of patients have been included, and the long-term efficacy and safety results cannot yet be fully evaluated. Intestinal implantation of a biodegradable stent is technically possible and relatively simple; however, there are still some drawbacks to be overcome. In particular, the
Table 2  Technical details and outcomes for the 11 patients with Crohn’s disease and significant gastrointestinal stenoses who underwent biodegradable stent insertion.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Site of stenosis</th>
<th>Ulcers at stenosis</th>
<th>Previous endoscopic dilation, number of procedures</th>
<th>Stenosis before stent insertion</th>
<th>Design of the stent</th>
<th>Dimensions of stent used</th>
<th>Dilation before stent insertion, mm</th>
<th>Follow-up</th>
<th>Outcome</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Diameter, mm</td>
<td>Length, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Transverse colon</td>
<td>Yes</td>
<td>1</td>
<td>7</td>
<td>50</td>
<td>A</td>
<td>27 – 25 – 20</td>
<td>80</td>
<td>18</td>
</tr>
<tr>
<td>2*</td>
<td>IAA</td>
<td>Yes</td>
<td>0</td>
<td>5</td>
<td>20</td>
<td>C</td>
<td>18 – 20</td>
<td>22 mo</td>
<td></td>
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<tr>
<td>3†</td>
<td>ISA</td>
<td>No</td>
<td>2</td>
<td>6</td>
<td>15</td>
<td>A</td>
<td>27 – 25 – 20</td>
<td>12</td>
<td>24 mo</td>
</tr>
<tr>
<td>4</td>
<td>IAA</td>
<td>No</td>
<td>2</td>
<td>8</td>
<td>40</td>
<td>C</td>
<td>20 – 20</td>
<td>22 mo</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>IAA</td>
<td>Yes</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>C</td>
<td>18 – 20</td>
<td>22 mo</td>
<td>Symptom-free†</td>
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<tr>
<td>6</td>
<td>Descending colon</td>
<td>Yes</td>
<td>0</td>
<td>7</td>
<td>30</td>
<td>B</td>
<td>23 – 18 – 23</td>
<td>60</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>Ileocecal valve</td>
<td>No</td>
<td>0</td>
<td>12</td>
<td>15</td>
<td>B</td>
<td>23 – 18 – 23</td>
<td>60</td>
<td>2 d</td>
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<tr>
<td>8</td>
<td>ITA</td>
<td>No</td>
<td>2</td>
<td>12</td>
<td>15</td>
<td>B</td>
<td>23 – 18 – 23</td>
<td>40</td>
<td>8 wk</td>
</tr>
<tr>
<td>9</td>
<td>IAA</td>
<td>No</td>
<td>3</td>
<td>8</td>
<td>15</td>
<td>C</td>
<td>20 – 20</td>
<td>15</td>
<td>12 mo</td>
</tr>
<tr>
<td>10</td>
<td>IAA</td>
<td>No</td>
<td>2</td>
<td>12</td>
<td>25</td>
<td>C</td>
<td>20 – 20</td>
<td>12 mo</td>
<td>Symptom-free</td>
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<tr>
<td>11</td>
<td>Sigmoid colon</td>
<td>No</td>
<td>2</td>
<td>10</td>
<td>45</td>
<td>C</td>
<td>20 – 20</td>
<td>12 mo</td>
<td>Symptom-free</td>
</tr>
</tbody>
</table>

IAA, ileo-ascending colon anastomosis; ISA, ileosigmoid anastomosis; NA, not applicable; ITA, ileo-transverse colon anastomosis.

*A second biodegradable stent was inserted 4 months after the first one because of symptomatic re-stenosis at the same site.

†Symptom-free after the further procedure.

‡After 2 months, the biodegradable stent was shortened endoscopically because of a chimney effect (see Fig. 4) and was passed spontaneously 5 days later.

§Due to a fixed, sharp bend at the sigmoid-descending colon junction.

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†Symptom-free after the further procedure.

‡After 2 months, the biodegradable stent was shortened endoscopically because of a chimney effect (see Fig. 4) and was passed spontaneously 5 days later.

§Due to a fixed, sharp bend at the sigmoid-descending colon junction.
rate of early migration of stents was rather high in this group (3/10 patients), but it may be possible to solve this by appropriate tailoring and further improvements in the design of the biodegradable stents. Sometimes it may be difficult to distinguish between focal/topical Crohn’s disease activity and other causes in an isolated intestinal stenosis (with or without ulcer) where there is an absence of systemic inflammatory response and/or other endoscopic signs of activity in other areas of the bowel. We believe biodegradable stents might be used in both situations.

Recently, two papers reported severe mucosal hyperplastic reaction (with overgrowth and/or ingrowth) after insertion of biodegradable stents into the esophagus [31,32]. This complication was not noticed in any of our patients; however, asymptomatic patients did not undergo further follow-up colonoscopy.

An ideal stent for benign stenoses would be one that has a large diameter, high expansion ratio, axial flexibility, optimal delivery system, withstands ingrowth, maintains luminal integrity, does not cause stent-induced mucosal or parenchymal injury, and does not need a repeat endoscopy for removal. Biodegradable stents seem to be an ideal way of achieving this goal in the future.

In conclusion, endoscopic introduction of biodegradable stents does not need a repeat endoscopy for removal. Biodegradable stents might be used in both situations.

**Acknowledgments**

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**Competing interests:** None

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