Drug-eluting/biodegradable stents

The ASGE Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methodology is used, performing a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported complications of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases data from randomized, controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors.

Technology Status Evaluation Reports are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the Committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through September 2010 for articles related to endoscopy by using the key words "gastroscope," "colonoscope," "echoendoscope," "duodenoscope," "choledochoscope," "ultraslim endoscope," "variable stiffness colonoscope," and "wide-angle colonoscope."

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INTRODUCTION

Metal and plastic stents have an established role in management of both benign and malignant strictures throughout the GI tract. Studies have demonstrated the clinical efficacy and safety in appropriately selected patients. Detailed reviews of commercially available stents have previously been published.[1-2] Alternative stent technology has been explored in an attempt to address some common problems including tissue ingrowth and need for removal when used in benign disease. This review discusses drug-eluting and biodegradable stents.

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BACKGROUND

A wide variety of drugs or biologically active agents, including antineoplastic agents, antithrombins, immunosuppressants, and tissue growth or inhibitory factors can be incorporated into stents to exert a desired physiologic effect.[3-4] The cardiovascular stent market remains the dominant driving force for research and development of both drug-eluting and biodegradable stents. The requirements for biodegradable or drug-eluting stents in the GI tract, however, are vastly different than for coronary stents. Although much less is currently known about the clinical utility or ideal stent designs for use in the GI tract, these have been a topic of preclinical and preliminary studies over recent years.

EMERGING TECHNOLOGY

Biodegradable stents in the esophagus

A case report and a small case series (including a total of 6 patients) demonstrated the feasibility of inserting a self-expandable stent made of a single wire of poly-L-lactide in a coil-spring configuration, designed to degrade over a 3 to 6 month period (InStent Inc, Eden Prairie, Minn).[5-6] Clinical results were inconsistent and suboptimal. Another biodegradable stent (Marui Textile Machinery Company Ltd, Osaka, Japan) made of machine-knitted poly-L-lactide monofilaments was developed more recently, with a configuration and mechanical radial force similar to those of commercially available esophageal stents.[7] Three subsequent reports by the same group of investigators demonstrated feasibility of use, with a low incidence of stent-related complications.[7-9] The largest cohort consisted of 6 patients undergoing treatment for benign esophageal strictures (caustic or anastomotic) and 7 patients undergoing prophylactic stenting following extensive endoscopic submucosal dissection (ESD) in an effort to prevent post-ESD strictures.[8] Although the stent was deemed successful based on the absence of symptoms or need for further dilatations in all the study pa-

tients, the majority (77%) of the stents had migrated out of the esophagus within 10 to 21 days of insertion, and only 3 patients had stents remain in position for more than 21 days. Because of this tendency for early stent migration in these 3 reports, the natural history of stent degradation within the esophagus and the tolerability of the degradation process over time were not adequately assessed.

In 2007, the first (and currently the only) biodegradable stent with regulatory clearance for use in the GI tract became available in Europe only, indicated for use in benign refractory esophageal strictures (peptic, anastomotic, caustic) and achalasia. This stent comes in several sizes, with stent body diameters ranging from 18 to 25 mm and fully deployed lengths of 60 to 135 mm. The stent requires compression and assembly onto a 9.4-mm (28F) delivery system immediately prior to clinical use. The stent is self-expandable and is composed of polydioxanone fiber, which is a semicrystalline biodegradable polymer belonging to the polyester family. According to the manufacturer (ELLA-CS Ltd, Hradec Kralove, Czech Republic), the results of unpublished in vitro and animal tests demonstrate that the radial resistive force of the SX-ELLA-BD stent remains intact for approximately 4 weeks, dropping to 50% of the original level by week 9. Following insertion of the stent into the esophagus, the earliest signs of degradation are discoloration and single breaks of the stent mesh. Integrity and radial force are maintained for approximately 6 weeks following implantation, and the average time to complete degradation of the stent is reported to be 11 to 12 weeks. More rapid degradation occurs with acid exposure, hence acid-suppressing therapy is recommended. As the stent degrades, small fragments of the stent may pass distally through the GI tract and are further degraded, absorbed, or eliminated.

Case series have described initial experience with the SX-ELLA-BD stent for treatment of a variety of esophageal strictures, including caustic,[10-12] peptic,[10,13-14] malignant,[13-15] anastomotic,[10,15-16] and radiation-induced strictures[10] as well as achalasia.[13] Clinical responses and outcomes were varied. In the largest cohort of patients with refractory benign esophageal strictures, 21 patients who had required an average of 2.2 endoscopic dilations per month underwent insertion of 25-mm SC-ELLA-BD stents.[10] There was 100% technical success and no intraprocedural complications. Postprocedural complications included severe thoracic pain (14%) sometimes lasting until the stent degraded, migration 4 to 7 weeks after placement (9.4%), and one case of significant tissue hyperplasia resulting in occlusion of the stent. In 19 patients, vestiges of the fragmented stent persisted in the esophagus at 3 months; the stents were completely eliminated by 6 months in all patients. After a median follow-up of 53 months, 45% of patients had significant relief of dysphagia and required no further therapy, whereas 55% failed to respond and required resumption of serial endoscopic dilations, albeit at less frequent intervals than they required before stenting. Other than the patient with hyperplasia-related stent occlusion, there were no long-term stent-related complications.

Recently, SX-ELLA-BD stents modified with a nonbiodegradable covering made from polyurethane were used in 5 patients with esophageal leaks or perforations (4 anastomotic dehiscence, 1 iatrogenic perforation).[17] Initial clinical success was achieved in 4 of 5 (80%). The single treatment failure was caused by the polyurethane coating, which deformed as the stent degraded and caused acute aphagia requiring endoscopic extraction. Stent migration occurred in 3 patients within 5 to 7 days, but because of the biodegradable nature, retrieval was not performed. One of the 3 patients required placement of additional biodegradable stents, and successful closure of the leak was still achieved.

Although total numbers of studied patients are small, published case series on SX-ELLA-BD stents encourage additional investigations into its use. However, this stent, not unlike commercially available self-expandable metal stents (SEMSs) and plastic stents, can induce significant hyperplastic tissue responses.[10,13,15-16,18] Efforts to define ways to prevent and treat this troublesome complication are ongoing.

Biodegradable stents in the pancreaticobiliary tract

Commercially available plastic and metal stents for the bile duct and pancreatic duct have many limitations, particularly when used for management of benign strictures. Although data suggest that endoscopic removal of covered SEMSs is feasible,[19-20] their removal is not approved by the Food and Drug Administration, requires additional endoscopic procedures, and may be associated with complications. Biodegradable stents have the potential to address these limitations.

Several animal trials of braided, woven, or helically configured biodegradable biliary stents have demonstrated feasibility of implantation, relative safety, and potential efficacy in a variety of experimental settings. Scenarios in which they have been studied include endoscopic[21] or surgical[22] placement into normal canine bile ducts, as reinforcement of hepaticojejunal[23-24] or common bile duct anastomoses,[25-26] for promotion of patency and growth of biliary epithelium within "neo-bile ducts" created by using explanted jugular vein grafts,[27-28] and management of cystic duct leaks following cholecystectomy.[29] However, there have been a limited number of reports on their use in humans. In 2001, Haber et al[30] published (in abstract form) interim results from a prospective, multicenter study of a prototype bioabsorbable biliary Wallstent (Boston Scientific, Natick, Mass) made of poly-L-lactic acid monofilaments woven into a tubular mesh stent configuration (stent diameter, 10 mm; delivery system diameter, 11F) in 50 patients with inoperable malignant extrahepatic bile duct obstruction. Safe and successful stent deployment was achieved in the majority of patients, but data regard-

ing overall complications, patency, and survival are not available, and the study has not been published in full form. Another recent study described use of a version of the SX-ELLA-BD esophageal stent modified for the biliary tree to treat refractory intrahepatic bile duct stenoses (centrally located) in 2 patients who had previously undergone surgical bilioenteric reconstructions.[31] Durable clinical resolution of the biliary strictures was reported with up to 2-years of follow-up.

In animal models, the histological changes in the duct and pancreatic parenchyma following placement of a biodegradable stent are reportedly negligible.[32] Adding barium sulfate to increase radiopacity of biodegradable stents helped facilitate both deployment under fluoroscopy and radiographic confirmation of complete degradation of the stent.[33-34] No human studies of pancreatic duct stenting with biodegradable stents have been performed.

Biodegradable stents in the small intestine and colon

Although use of enteral stents is an area of clinical interest, limited published information regarding biodegradable enteral stents exists. In one case report, 3 patients with Crohn's disease with stenosing complications (2 anastomotic strictures and 1 primary colonic Crohn's stricture) underwent endoscopy with balloon dilatation of the stenoses followed by placement of SX-ELLA-BD stents.[35] The stents degraded over a mean of 4 months. Despite one mechanical complication requiring endoscopic modification of the stent, no stent migrations or major complications occurred. However, long-term efficacy and safety data remain unknown.

Drug-eluting stents in the GI tract

Drug-eluting stents are composed of 3 main elements: a stent platform, a drug-carrier, and an active drug.[36]

In vitro and in vivo studies (the latter using drug-coated SEMSs) have demonstrated that local exposure to paclitaxel, 5-fluorouracil, and gemcitabine can induce local responses when placed in contact with both benign and malignant GI tract tissues.[37-44] To date, there are only a few small published case series in humans. These demonstrated that partial responses in unresectable cholangiocarcinoma can be achieved with a carboplatincoated percutaneous biliary tube,[45] and endoscopically placed drug-eluting SEMS may be associated with improved stent patency and overall survival in patients with extrahepatic cholangiocarcinoma.[46]

In the latter trial, 21 patients underwent placement of paclitaxel-coated biliary SEMSs for presumed extrahepatic cholangiocarcinoma; mean follow-up was 329 days.[46] There were no paclitaxel-specific toxicities, and systemic concentrations resulting from paclitaxel absorption were relatively low. Paclitaxel improved mean stent patency rates and overall patient survival compared with historical controls treated with conventional SEMSs. However, limitations of the trial include the use of a historic rather than an internal control arm, inclusion of patients (43%) without histopathologic confirmation of malignancy, the nonrandomized design, and an overall stent occlusion rate of 43%.

POTENTIAL APPLICATIONS

There are many clinical scenarios in which biodegradable stents may have potential advantages. Because biodegradable stents do not require endoscopic removal, even if they migrate, they may prove to be more useful than conventional SEMSs or plastic stents in many situations:

- Management of refractory benign stenoses and leaks (particularly if covered stents that are completely biodegradable become available)
- Palliation of malignant obstruction in patients undergoing chemoradiation for esophageal or pancreaticobiliary cancers
- When uncertainty exists about the diagnosis of malignancy (eg, indeterminate bile duct strictures) or about an individual's candidacy for surgery
- Prophylactic placement to prevent iatrogenic GI tract strictures in high-risk patients, such as those undergoing extensive endoscopic resections, enteral anastomoses, or pancreaticobiliary reconstructions

In theory, an enormous array of biologically active agents and drugs could be incorporated into drug-eluting stents. Examples include chemotherapeutic drugs or other biologic modulators, such as radiation-sensitizing agents and mediators of angiogenesis, proliferation, inflammation, or fibrosis. Although the field is still in its infancy, evolution of drug-eluting stents could allow highly individualized, tailored, targeted therapy for a range of benign and malignant medical conditions.

AREAS OF FUTURE RESEARCH

The available series on drug-eluting and biodegradable stents in the GI tract are small series demonstrating technical feasibility and relative safety of these technologies. Additional reports from European endoscopists with experience using the SX-ELLA-BD stent are forthcoming, including trials comparing them to commercially available plastic stents and SEMSs (personal communication). Biodegradable GI tract stents probably will become available in the United States within the next few years. As with any emerging technology, it is advisable that initial use of these devices be limited to endoscopy centers with expertise in product assessment and development, because several important considerations need to be addressed before they reach the mainstream. Examples include the need for the following:

- Larger, prospective, well-designed studies must demonstrate long-term efficacy and safety of biodegradable

stents at each applicable location within the GI tract and for a broad range of benign and malignant indications.
- Additional research is required to better understand the mechanisms of controlled-drug release and systemic absorption from drug-eluting GI tract stents, the complex interactions that occur, including drug-host response interactions and the effect that various drugs may have on the physicochemical and mechanical properties of stent platforms and biopolymers.[36,47-49]

SUMMARY

A biodegradable stent for GI applications is commercially available in Europe. In the upcoming years, these types of stents may enter the U.S. market. They have potential advantages over currently used plastic or metal stents for a range of clinical applications. Significant research on these as well as other new stent designs (eg, drug-eluting stents) is required. As with any novel technology, a tempered and evidence-based approach will be key in successfully establishing the role of these devices in clinical practice.

DISCLOSURE

J. Tokar is a consultant for Boston Scientific and is a speaker for and recipient of an educational grant from Fujinon. D. Pleskow is a consultant for Boston Scientific and is on the medical advisory board of Beacon Endoscopic. L.M. Wong Kee Song has received research support from Olympus and Fujinon. No other financial relationships relevant to this publication were disclosed.

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; ESD, endoscopic submucosal dissection; SEMS, self-expandable metal stent.

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