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First-in-Human Implantation of a Fully Bioabsorbable Drug-Eluting Stent: The BVS Poly-L-Lactic Acid Everolimus-Eluting Coronary Stent

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The first-in-human fully bioabsorbable drug-eluting stent (BVS poly-L-lactic acid everolimus-eluting coronary stent) implantation was performed at Auckland City Hospital, New Zealand as part of the ABSORB trial. There were no adverse events in-hospital or by 1 month. A stent that supports the vessel when needed, delivers an antiproliferative drug then disappears has theoretical advantages with regard to CT and MRI compatibility, restored vessel vasomotion, and facilitated future percutaneous intervention or surgical grafting to the treated site. © 2006 Wiley-Liss, Inc.

Key words: stent; drug-elution; bioabsorbable; polyactic acid; internal hyperplasia

INTRODUCTION

In contrast to a permanent metal stent, a completely absorbable stent may allow the vessel to react normally to pulsatile flow, to positively remodel and to respond normally to factors released by endothelium. A polymer stent is potentially compatible with imaging by contemporary multislice computed tomography and magnetic resonance that will play an increasing role in the future. The stented segment may be suitable for future surgical revascularization, unlike vessels that have undergone extensive metal stent deployment. A bioabsorbable poly-L-lactic acid (PLLA) stent without an antiproliferative drug has, in humans, had outcomes similar to those after implantation of bare metal stents with 18% of patients needing a repeat revascularization by 4 years [1,2]. The BVS bioabsorbable stent (Abbott Vascular, Santa Clara, CA) constructed from PLLA performs acutely like a metal stent, has ceased to splint the vessel by 1 year and is expected to completely absorb by 2–3 years [3]. In addition, it releases everolimus that has been clinically proven to reduce restenosis [3–5].

CASE REPORT

A 64-year-old nonsmoking man with treated dyslipidemia, gastroesophageal reflux disease, a history of colectomy for carcinoma of the bowel 5 years previously, presented with a 3-month history of class II angina. He developed angina associated with 1.5–2 mm ST segment depression during stage II of a Bruce Protocol treadmill exercise test. Angiography revealed normal left ventricular contractility with an ejection fraction of 84%. There was a severe lesion in the mid left anterior descending coronary artery (LAD). There was mild disease elsewhere including proximal LAD and severe disease in the small second diagonal artery.

On March 7, 2006 at Auckland City Hospital, he was the first patient enrolled in the ABSORB Trial when a 3 × 12 mm BVS PLLA everolimus-eluting coronary stent was implanted in his mid LAD. The trial had been previously approved by the Auckland Regional Ethics Committee and the patient had provided written informed consent. In addition to his regular aspirin therapy, he was pretreated with clopidogrel, 600 mg orally. Anticoagulation was with Bivalirudin and 200 μg of nitroglycerin were administered by the intracoronary route before baseline angiography, after predilatation, after stent deployment, before the intracoronary ultrasound study and before final angiography. After baseline angiography (Fig. 1A), through a 7F XB 3.5 guide, over an 0.014 in. BMW wire (Abbott Vascular, Santa Clara, CA), the lesion was predilated with a 2.5 × 9-mm Maverick bal-

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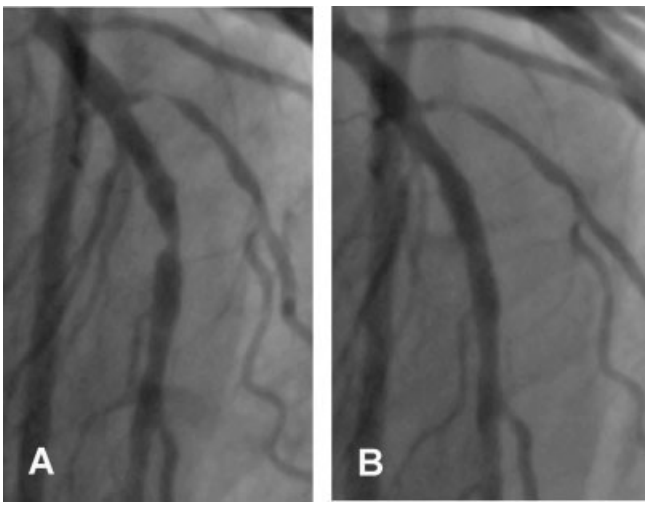

Fig. 1. Coronary angiography before (A) and after (B) BVS bioabsorbable everolimus-eluting stent implantation.

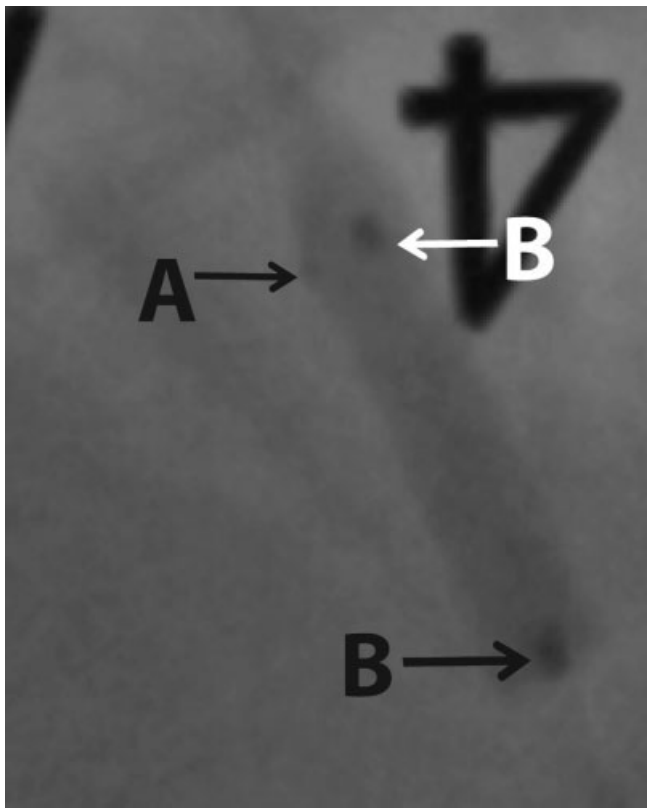

Fig. 2. Stent deployment. The BVS stent has metallic markers (A) at each end and the delivery balloon has markers (B).

loon (Boston Scientific, Natick, MA). The trial stent was deployed with a single inflation at 12 atm (Fig. 2). Intracoronary ultrasound recordings were made for virtual histology and palpography analysis and repeat angiography was recorded (Fig. 1B). The procedure was well tolerated without chest pain or hemodynamic disturbance. There was no evidence of any myocardial injury on subsequent troponin and creatine kinase enzyme measurement.

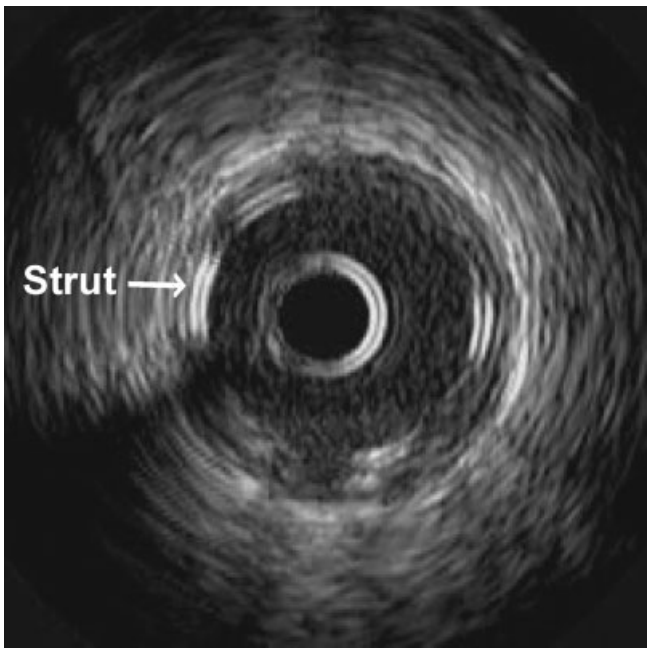

Fig. 3. Intracoronary ultrasound image of a BVS stent. The parallel echoes represent reflected ultrasound from the blood/stent and stent/tissue interfaces. Because ultrasound can pass through a polymer stent in contrast to a metal stent, there is no acoustic shadowing behind the stent struts.

The intracoronary ultrasound (Fig. 3) shows a fully expanded stent with the polymer struts represented by parallel layers of echoes and without the acoustic shadowing characteristic of metallic stents. At 1-month follow-up the patient was well and without angina. He will return for clinical and imaging follow-up at prespecified time intervals out to 5 years and will take daily Clopidogrel 75 mg for 6 months and Aspirin $\geq$75 mg indefinitely.

DISCUSSION

The BVS stent has a bioabsorbable polymer backbone of PLLA coated with the bioabsorbable polymer, poly-D,L-lactic acid (PDLLA) that contains and controls the release of the antiproliferative drug, everolimus. Polylactide polymers and copolymers are approved for use in hundreds of clinical situations ranging from absorbable sutures, orthopedic plates, and screws, to dermal filler in cosmetic surgery [3].

The chemical structure of PLLA/PDLLA is repeating units as shown in Fig. 4. In the absorption process, the

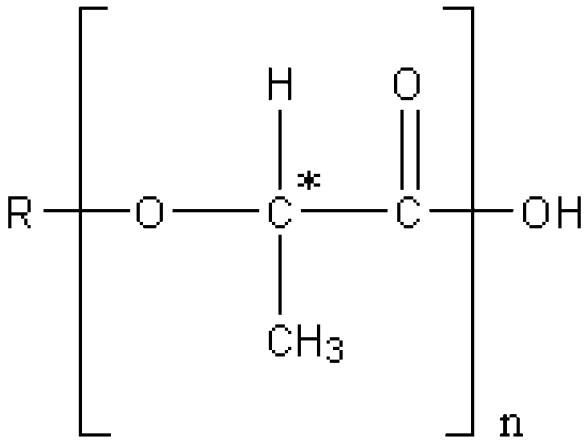

Fig. 4. Chemical structure of PLLA.

long chains of PLLA/PDLLA become shorter as bonds between the repeating units are hydrolysed producing lactic acid that is metabolized via the Krebs cycle and small particles <2 μm diameter that are phagocytosed by macrophages [3]. The time for complete absorption of the polymer backbone is predicted from preclinical studies to be about 2–3 years whereas the polymer coating is much more rapidly absorbed. In preclinical studies the artery is splinted by the stent at 6 months and by 12 months, the stented vessel is able to contract in response to intracoronary acetylcholine [3].

While there have been reports of marked inflammatory reactions to absorbable polymers [6] there is no experimental evidence of excessive inflammation with the BVS bioabsorbable stent [3]. In a nonatheromatous pig coronary model and a rabbit iliac model, at 6 and 9 months there was a thin well healed neointima with compact smooth muscle cells in a proteoglycan/collagen matrix [3]. There was complete luminal endothelialization by 28 days in the porcine model and lumens were widely patent. There was no evidence of medial necrosis or thinning. Overall inflammation was minimal and was similar at 3 and 6 months to that after control Cypher (J&J, Miami, FL) stent implantation. At 9 and 12 months inflammation was less than after Cypher control [3]. Based on the presence of fibrin adjacent to BVS stent struts, a maintained drug effect was observed at 28 days, but was largely gone at 90 and180 days [3].

The safety of PLLA is supported by the benign vascular response following human femoral artery puncture site sealing with the AngioSeal femoral closure device.

The safety of PLLA is further supported by the clinical outcomes of the first-in-human coronary implantation of the Igaki–Tamai PLA polymer stent [1,2]. This stent did not have an antiproliferative drug coating and major adverse cardiac events at 4-years follow-up in the 50 patients with 63 lesions were similar to those expected after bare metal stent implantation in that there was one in-hospital subacute stent thrombosis causing a Q-wave myocardial infarction, one noncardiac death, 18% repeat PCI and no surgical revascularization [1,2].

The coating polymer that contains and controls the drug release is PDLLA and is the same polymer used for the Abbott Champion drug-eluting stent project and used in the FUTURE trials [7].

The antiproliferative drug used on the BVS stent, everolimus (Novartis) is a novel semisynthetic macrolide immunosuppressant, obtained through chemical modification of sirolimus. It has the same mechanism of action as sirolimus. The release rate of everolimus from the BVS stent (80% by 30 days) is similar to the release rate from the XIENCE^{TM} V everolimus-eluting coronary stent and similar to the release rate of sirolimus from the Cypher stent [3]. In preclinical studies, tissue retention of everolimus released from the BVS stent is similar to that of sirolimus released from the Cypher stent [3]. The dose of everolimus on the BVS stent is 8.2 μg/mm [3].

The efficacy and safety of the drug, everolimus on either a stainless steel or cobalt chromium backbone are apparent from the FUTURE and SPIRIT first trials, respectively [4,5,7]. The basic design of the BVS stent is circumferential hoops of PLA with strut thickness of 150 μm that are linked directly or by straight bridges. At both ends of the stent there are two adjacent radio-opaque metal markers [3]. These are clearly visible on fluoroscopy and facilitate precise postdilatation because stent ends can be precisely located on fluoroscopy (Fig. 2).

In our experience, the BVS stent performs like a bare metal stent. The crossing profile of the BVS at 1.4 mm is a little more than the bare metal B × velocity and less than the original MULTI-LINK. We measured radial strength in a water bath at 37°C by recording with intravascular ultrasound the cross-sectional area changes occurring with incremental pressure changes. Radial strength was in the same order as that of a MULTI-LINK stent. Testing by flat plate compression shows similar results [3]. While the MULTI-LINK stent had relatively low radial strength compared with other metal stents, clinical outcomes were very good even with long stents [8].

The balloon delivery system is the same as used for the Abbott MULTI-LINK VISION, ZETA, and XIENCE V stents.

The intracoronary ultrasound appearance after polymer stent implantation (Fig. 3) differs from that after metal stent implantation. A polymer strut appears as two-parallel lines because ultrasound is reflected from the blood/polymer interface then from the polymer/tissue interface as the ultrasound passes through the strut. Because the ultrasound is not completely reflected in contrast with a metal stent, some of the beam passes through the polymer stent, and thus there is no acoustic shadowing behind the struts.

In summary, this is a report of first-in-human implantation of a fully bioabsorbable drug-eluting stent. The early performance of the BVS PLLA everolimus-eluting coronary stent appears similar to that of metallic stents. Absorbable stents may represent a significant step forward in the evolution of percutaneous coronary intervention.

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