Angiographic and Clinical Outcomes of a Pharmacokinetic Study of Sirolimus-Eluting Stents

— Lesson From Restenosis Cases —

Masato Nakamura, MD; Masamichi Wada, MD; Hisao Hara, MD; Ken Kozuma, MD*; Yoritaka Otsuka, MD**; Shunichi Miyazaki, MD**

Background A pharmacokinetic (PK) study was conducted to evaluate sirolimus-eluting stents (SES) in Japanese people, representing the first clinical trial of the use of drug-eluting stents in Japan.

Methods and Results The PK study was conducted in 20 patients with 30 lesions treated with sirolimus-coated BX Velocity stents. All lesions were treated with a single SES (3×18 mm). Angiographic follow-up was performed at 8 months after SES implantation, and the clinical outcomes were evaluated at 1 year in all cases. All procedures were successful, and all patients were discharged without any adverse cardiac events. The total restenosis rate was 10% (3 lesions) and target vessel revascularization was performed in those 3 cases (15%). Restenoses occurred at the proximal and distal stent margins. Intravascular ultrasound examination of restenosis cases revealed abundant plaque burden at the stent edges even though the luminal area was preserved.

Conclusions The sirolimus-eluting BX Velocity stent is safe and useful for Japanese patients with coronary artery disease. However, restenosis at proximal stent edge seems to be a problem. (Circ J 2005; 69: 1196–1201)

Key Words: Drug eluting stent; Intravascular ultrasound; Restenosis

Restenosis is the main limitation of percutaneous coronary intervention (PCI), but the introduction of drug-eluting stents (DES) is a breakthrough development. Clinical trials of DES have reported a markedly decreased rates of restenosis and revascularization compared with bare metal stents (BMS),^{1–6} but the efficacy of DES in Japanese people is still unclear.

Prior to getting approval for the sirolimus-eluting stent (SES: Cypher stent, Cordis Corp, a Johnson&Johnson Company) in Japan, a pharmacokinetic (PK) study evaluating the PKs of sirolimus in Japanese patients and the 1-year clinical outcomes was conducted.⁷

Methods

Study Subjects

The PK study was the first clinical trial of the SES in Japan, and its aim was to evaluate the PKs of sirolimus in Japanese patients and to evaluate early and late clinical outcomes. It was a nonrandomized open trial, comprising 20 patients with 30 lesions who underwent implantation of SES. The patients were all symptomatic and/or had functionally significant de novo native coronary artery disease. Patients were excluded from this study if they had (1) acute myocardial infarction, (2) unstable angina (Braunwald III

B, III C), (3) bifurcation lesions, (4) ostial lesions, (5) left main trunk disease, (6) severe calcification, (7) chronic total occlusion, (8) renal dysfunction (serum creatinine >3.0 mg/dl) or liver dysfunction, (9) proximal reference diameter <2.5 mm, (10) allergy to antiplatelet drugs, heparin and sirolimus, (11) extreme bending lesion, (12) left ventricular ejection fraction <25%, (13) cardiac transplantation or (14) another stent within 5 mm of target lesion. The ethical committee at each participating institute approved the protocols, and all patients gave written informed consent.

Procedure

Before angioplasty, heparin was given intravenously and titrated to maintain an active clotting time more than 250 ms. All patients received a BX velocity stent (3×18 mm) loaded with a total sirolimus doses of 150 µg. All lesions were pre-dilated before stent implantation and adequate post dilatation was performed. All patients received aspirin (200 mg/day indefinitely) and ticlopidine (200 mg/day) from 3 days before the procedure and continued daily for 3 months after SES implantation.

Quantitative Coronary Angiography (QCA)

Detailed QCA parameters of the target lesion were evaluated before and after the procedure and at the time of angiographic follow-up using a computer-based system (QCA-CMS 5.1, MEDIS, Leiden, the Netherlands) and an independent observer at Toho University Ohashi Medical Center. This QCA software allows us to also measure automatically all parameters for 5 mm proximal and distal to the stented segment. At the follow-up analysis, in-stent restenosis (ISR) was defined as a diameter stenosis >50% within the stent segment. In-segment restenosis was defined as >50% either within the stented segment or within

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Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, *Department of Cardiology, Teikyo University School of Medicine, Tokyo and **Department of Cardiology, National Cardiovascular Center, Suita, Japan

Mailing address: Masato Nakamura, MD, Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, 2-17-6 Ohashi, Meguro-ku, Tokyo 153-8515, Japan. E-mail: masato@oha.toho-u.ac.jp

Table 1 Patients Characteristics

<i>n</i>	20
Age (years)	64.2±9.9
Height (cm)	162.1±8.3
Weight (kg)	65.3±12.6
Male, <i>n</i> (%)	16 (80)
Risk factors	
Hypertension, <i>n</i> (%)	16 (60)
Hyperlipidemia, <i>n</i> (%)	11 (55)
Diabetes mellitus, <i>n</i> (%)	12 (60)
Smoking, <i>n</i> (%)	13 (65)
Obesity, <i>n</i> (%)	7 (35)
Target vessel, <i>n</i> (%)	
LAD	12 (40)
LCX	6 (20)
RCA	12 (40)
Ejection fraction (%)	61.0±11.2
Previous MI, <i>n</i> (%)	3 (15)
Previous PCI, <i>n</i> (%)	7 (35)
Previous CABG, <i>n</i> (%)	0
Lesion type (ACC/AHA), <i>n</i> (%)	
A/B1	24 (80)
B2/C	6 (20)

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACC, American College of Cardiology; AHA, American Heart Association.

5 mm proximal or distal to the stent segment. In-stent late lumen loss was defined as the difference between the minimal luminal diameter (MLD) immediately after the procedure and the MLD at follow-up.

Intravascular Ultrasound (IVUS) Studies

IVUS studies conducted at the end of the procedure and at the time of follow-up used a 30- or 40-MHz transducer-tipped catheter (Ultra-cross 3.2Fr, Atlantis SR3.0Fr and Atlantis SR Plus 2.5Fr, Boston Scientific, Sunnyvale, CA, USA). IVUS images were acquired during motorized pull-back at a constant speed of 0.5 mm/s and were recorded on VHS video tape. Acquisition of IVUS images was started at least 1 cm distal to the stent and ended at least 1 cm proximal to stent.

Results

Baseline Characteristics

The patient and lesion profiles are summarized in Table 1. The mean age was 64.2±9.9 years, and a high prevalence of patients with diabetes mellitus.

Procedural Data

The mean lesion length and reference diameter were 12.1±3.8 mm and 2.67±0.58 mm, respectively. Stents were deployed with a mean pressure of 14.7±3.7 mmHg, and dilated by post dilatation balloon with a pressure of 15.4±3.3 mmHg. Procedural success was achieved in all patients, and all cases were discharged without any adverse cardiac events.

Angiographic Follow-up Data

Angiographically analyzed data are shown in Table 2. In-segment and ISR per lesion occurred in 3 (10%) and 2 lesions (6.6%), respectively. Focal-type restenosis occurred at the proximal edge of the stent (Fig 1) in 1 case, and total-occlusion-type ISR occurred in 1 case that involved 2 SES

Table 2 Angiographic Data

In-stent analysis	
Reference vessel (mm)	2.67±0.58
MLD (mm)	
Pre	0.99±0.48
Post	2.73±0.47
Follow-up	2.46±0.66
%DS	
Pre	62.8±16.4
Post	12.1±5.71
Follow-up	18.9±17.6
Late loss	0.27±0.69
In-segment analysis	
Reference vessel (mm)	2.67±0.58
MLD (mm)	
Pre	0.99±0.48
Post	2.59±1.64
Follow-up	2.10±0.70
%DS	
Pre	62.8±16.4
Post	25.2±12.1
Follow-up	31.5±21.5
Late loss	0.50±1.52
Late loss at proximal margin	0.17±0.75
Late loss at distal margin	0.21±0.63
Angiographic restenosis	
In-stent	2 (6.6%)
In-segment	3 (10%)

Continuous variables are presented as mean (SD).

Late loss, difference between MLD at 8 months and MLD after procedure. MLD, minimum lumen diameter; DS, diameter stenosis.

implantations (Fig 2). Late luminal loss was 0.27±0.69 mm in-stent, and 0.50±1.52 mm in-segment.

One-Year Outcome

Ticlopidine was discontinued in 2 cases because of rash and abnormal laboratory test values, but with no adverse events. At 1-year follow-up, none of the cases was complicated by stent thrombosis. There were 3 major adverse cardiac events (15%) during the follow-up period, but no deaths or myocardial infarctions, and only 1 target lesion revascularization (TLR) or target vessel revascularization. Two cases complicated by angiographic restenoses were successfully treated by additional stenting at 10 months, and another case had target vessel revascularization of the proximal stent segment at 1 year. These cases were asymptomatic, and revascularization was indicated by a positive stress test.

Insights of the TLR Cases From IVUS and Angiographic Examinations

Stent Edge Restenosis Case IVUS assessment after DES deployment revealed that the percent plaque area (%PA) at the proximal stent edge was 64.8%, and plaque area had increased from 10.5 mm² to 13.6 mm² (Figs 4,5).

Total-Occlusion-Type ISR Case SES implantation was performed for a 99% stenosed proximal right coronary artery (RCA) lesion and a 75% mid RCA lesion (Fig 3). Follow-up angiography revealed that the RCA was totally occluded in the segment proximal to the SES. Angiography after recanalization of the occluded proximal RCA with a small balloon (1.5 mm in diameter) revealed that the in-stent segment was fully patent. A side branch within the DES was open even though RCA was totally occluded and not being filled by collateral flow from the left coronary artery (Fig 3). IVUS examination revealed that the plaque

Fig 1. Angiograms of proximal stent edge restenosis after the procedure (Right) and at follow-up (Left). There is focal restenosis (arrow) at the proximal stent edge. White line represents sirolimus-eluting stent implanted in the left circumflex artery.

Fig 2. Intravascular ultrasound images of proximal stent edge restenosis after the procedure and at follow-up. After stent deployment, the plaque area (PA) at the stent edge is 10.5 mm² and it increased to 13.6 mm² at the end of the follow-up period. LA, lumen area; VA, vessel area.

burden in the proximal stent segment was more than 50% (Fig 6). The serial IVUS examination also demonstrated that luminal narrowing at the stent edge, not intimal hyperplasia, was contributing to the narrowing of the vessel area (Fig 7).

Discussion

This study is the first Japanese experience with implantation of the sirolimus-coated BX Velocity stent. We report (1) procedural success in all cases without any adverse event during hospitalization; (2) restenosis at the proximal

and distal margins of the SES; (3) the presence of a large plaque burden adjacent to the stent on IVUS assessment might be a predictor of stent edge restenosis.

Edge Restenosis

Restenosis occurred not within the stent but at its margins, which concurs with the findings of the Sirius trial, which reported that in-segment restenosis occurred at a higher frequency at the proximal margin of the stent than at the distal margin or in the body of the stent.² It has been reported that 87% of the restenoses were focal type, and that total occlusion was extremely rare;² However, in the

Fig 3. Angiograms of the case of total-occlusion-type in-stent restenosis before (a) and after the procedure (b), at follow-up (c), and after recanalization (d). Follow-up angiography revealed occlusion of the right coronary artery proximal to the stented segment. The angiogram after recanalization (d) shows that the lumen and side branch of the sirolimus-eluting stent are open. There is a “candy-wrapper appearance” to this angiogram.

Fig 4. Post-procedural intravascular ultrasound of the case of total-occlusion-type in-stent restenosis shows abundant plaque burden even the lumen is clear. LA, lumen area; PA, plaque area.

Fig 5. Follow-up (F/u) and post-procedural intravascular ultrasound show lumen narrowing but without an increase in the plaque area.

present study there was 1 case of total-occlusion-type stent restenosis.

Mechanism of Restenosis With DES

Even though the mechanism of restenosis after DES implantation is difficult to elucidate, our experience in this PK trial lead us to speculate on some likely reasons. In the case of total-occlusion-type restenosis, angiography showed that the SES was fully patent, and its internal side branch was still open, even after the coronary artery was totally occluded. This finding clearly demonstrates the efficacy of the SES in preventing intimal hyperplasia especially within the stent. Therefore, the SES may modify the pattern of restenosis from the diffuse ISR that occurs with BMS implantation to edge restenosis. As a result, the proportion of focal-type restenosis to all restenosis cases might increase with more widespread use of SES. In a serial IVUS study of Palmaz-Schatz stents performed by Hoffmann et al⁸, the dominant periprocedural predictor of stent margin restenosis was the plaque burden of the adjacent reference segments. Although it has not been demonstrated that plaque burden at the stent edge is also a predictor for edge restenosis with DES, in the present cases of restenosis with a SES, the post-procedural %PA adjacent to the proximal edge was more than 50%, even though the lumen was well preserved. Thus, our findings suggest that incomplete coverage by the SES may be involved in the occurrence of stent-edge restenosis. Because it is unclear what %PA is small enough to prevent the restenosis, accumulation of more data is required. Another potential explanation is procedural factors such as geographic miss. Regarding the edge effect of a radioactive stent, Albiero et al⁹ suggested

that it arises from a combination of 2 factors: (1) a low dose of radiation at the stent margin and (2) an aggressive approach to stenting as indicated by a high balloon-to-artery ratio. Angiolillo et al also suggested that radioactive stents and DES share many common features and that lessons learned from intracoronary brachytherapy should be applied to the DES era.¹⁰ They suggested that axial geographic misses because of inadequate stent size may be another reason for the edge effect.

It is difficult to elucidate the mechanism for the margin stenosis shown in Fig 3. Because significant intimal hyperplasia (increase in PA during follow-up) was not observed at the stent edge, it is possible that vessel narrowing is associated with this angiographic finding and would be consistent with a recently published report that attributed remodeling to edge restenosis after SES implantation.¹¹ Such vessel narrowing could contribute to insufficient coronary flow. Another explanation is that this vessel shrinkage represents an allergic reaction, as Virmani et al¹² suggested. However, this is no more than speculation and it is apparent that a variety of factors are involved in margin stenosis.

Clinical Implications

Since the initial report of the Sirius trial, much attention has been paid to edge restenosis after DES deployment and as a result, an optimal stenting technique for DES has been recommended: (1) avoid aggressive predilatation, (2) avoid post-dilatation outside the stent, (3) full coverage of the lesion, and (4) no gap between stents.^{2,13,14} Our results from the PK trial indicate that procedural factors, especially stent length, also could be important in determining the long-term outcome.

Study Limitations

Stent thrombosis was not a complication in this study, which suggests the efficacy and safety of ticlopidine in preventing stent thrombosis in the setting of SES implantation. However, this was an observational study of a small number of subjects. Long-term follow-up data are required to confirm the durability of this type of stent. Additionally, the long-term outcomes may have been affected by the study protocol in which the available sizes and number of stents was limited.

Conclusion

Sirolimus-coated BX Velocity stents are safe and feasible to use in Japanese patients with coronary artery disease. Neointimal growth within the stent was completely inhibited at 8 months after PCI. However, edge restenosis may occur under some conditions and the mechanisms of this phenomenon remains unclear. Subsequent investigation and additional information are required to better understand the mechanism of restenosis with SES deployment.

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