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Lack of Neointimal Proliferation After Implantation of Sirolimus-Coated Stents in Human Coronary Arteries

A Quantitative Coronary Angiography and Three-Dimensional Intravascular Ultrasound Study

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Background—Restenosis remains an important limitation of interventional cardiology. Therefore, we aimed to determine the safety and efficacy of sirolimus (a cell-cycle inhibitor)-coated BX Velocity stents.

Methods and Results—Thirty patients with angina pectoris were electively treated with 2 different formulations of sirolimus-coated stents (slow release [SR], n=15, and fast release [FR], n=15). All stents were successfully delivered, and patients were discharged without clinical complications. Independent core laboratories analyzed angiographic and 3D volumetric intravascular ultrasound data (immediately after procedure and at 4-month follow-up). Eight-month clinical follow-up was obtained for all patients. There was minimal neointimal hyperplasia in both groups (11.0±3.0% in the SR group and 10.4±3.0% in the FR group, P=NS) by ultrasound and quantitative coronary angiography (in-stent late loss, 0.09±0.3 mm [SR] and −0.02±0.3 mm [FR]; in-lesion late loss, 0.16±0.3 mm [SR] and −0.1±0.3 mm [FR]). No in-stent or edge restenosis (diameter stenosis ≥50%) was observed. No major clinical events (stent thrombosis, repeat revascularization, myocardial infarction, or death) had occurred by 8 months.

Conclusions—The implantation of sirolimus-coated BX Velocity stents is feasible and safe and elicits minimal neointimal proliferation. Additional placebo-controlled trials are required to confirm these promising results. **(*Circulation*. 2001; 103:192-195.)**

Key Words: stents ■ restenosis ■ angioplasty

Restenosis remains a vexing problem of percutaneous intervention. The most promising approach to prevent restenosis has been the application of intracoronary radiation[1]; however, some relevant side effects (edge restenosis and late thrombosis) have been reported.[2,3] Numerous pharmacological approaches to reduce restenosis have failed, possibly due to insufficient local drug concentrations.[4] Delivering medication directly to the site of vascular injury via polymeric-coated stents is a rational approach to achieve adequate local drug delivery.[5,6]

Sirolimus (Rapamune), a natural macrocyclic lactone, is a potent immunosuppressive agent that was developed by Wyeth-Ayerst Laboratories and approved by the Food and Drug Administration for the prophylaxis of renal transplant rejection in 1999.[7] Sirolimus binds to an intracellular receptor protein and elevates p27 levels, which leads to the inhibition of cyclin/cyclin-dependent kinase complexes and, ultimately, induces cell-cycle arrest in the late G1 phase. It inhibits the proliferation of both rat and human smooth muscle cells in vitro[8,9] and reduces intimal thickening in models of vascular injury.[10–12] However, the effects of the local administration of sirolimus in a coated stent in humans have not been reported.

The aims of this pilot study were to assess (1) the feasibility and safety of implanting 2 different formulations of the sirolimus-coated BX Velocity stent in atherosclerotic human coronary arteries and (2) the impact of the stents on neointimal proliferation.

Methods

From December 1999 to February 2000, a single sirolimus-coated BX Velocity stent was successfully implanted in each of 30 consecutive patients with coronary artery disease. The stent is a

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laser-cut, 316L stainless steel, balloon-expandable stent that contains a fixed amount of sirolimus per unit of metal surface area (140 μg of sirolimus per cm^2).

Sirolimus was blended in a mixture of nonerodable polymers that have been used clinically in bone cements, ocular devices, and a drug-releasing intrauterine device.[13,14] Fifteen patients received a fast release (FR) formulation (<15-day drug release), and 15 received a slow release (SR) formulation (≥28-day drug release).

Procedure

All stents were 18 mm long and 3.0 to 3.5 mm in diameter. After predilatation of the target lesion, stents were deployed with high-pressure (>14 atm) postdilatation guided by intravascular ultrasound (IVUS). All patients received aspirin (325 mg/d, indefinitely), which was started at least 12 hours before the procedure, and clopidogrel (300 mg immediately after stent implantation and 75 mg/d for 60 days). The protocol was approved by the Medical Ethics Committee of the Institute Dante Pazzanese of Cardiology, and informed consent was obtained from every patient.

Quantitative Measurements

Quantitative coronary angiography (QCA) and IVUS imaging were performed immediately after the procedure and at 4-month follow-up in all patients after a bolus infusion of intracoronary nitrates. IVUS images were acquired using motorized pull-back at a constant speed of 0.5 mm/s. Quantitative angiographic and volumetric IVUS analyses were performed by independent core laboratories (Brigham and Women's Hospital, Boston, Mass, and Cardialysis BV, Rotterdam, The Netherlands, respectively).[15–17] Three segments were selected for volumetric IVUS analysis: the stented segment (18 mm long) and 2 edge segments that were axially 5 mm proximal and distal to the stent margins.

Statistical Analysis

Continuous variables are expressed as mean±SD. Comparisons between postintervention and follow-up measurements were performed with a 2-tailed paired *t* test. Comparisons between groups were performed using an unpaired Student's *t* test. $P<0.05$ was considered statistically significant.

Results

Twenty-six patients had stable angina and 4 patients had unstable angina. Their mean age was 57.9±10 years (SR) and 55.1±7 years (FR); 63% of the patients in each group were male. The incidence of prior myocardial infarction was 33.3% (SR) and 53.3% (FR), and 14% (FR) and 26% (SR) of the patients were diabetics. All stents were implanted successfully, and all patients were discharged without complications 24 hours after treatment. Creatine kinase and creatine kinase-MB levels, sampled at 6 and 18 hours after the procedure, were within the normal range in all patients.

Angiographic and volumetric IVUS data are presented in Tables 1 and 2. No patient approached ≥50% vessel narrowing by QCA or IVUS, and only 3 patients had >15% intimal hyperplasia (IH) by IVUS (Figure 1). In both the edge segments and in the stented segment, lumen loss detected by IVUS was minimal (Figure 2). All patients completed 4 months of angiographic and 8 months of clinical follow-up. There were no repeat revascularizations, stent thromboses, or major clinical events (cerebrovascular accident, myocardial infarction, or death).

Discussion

This is the first human experience with the implantation of sirolimus-coated BX Velocity stents. The absence of adverse events for up to 8 months of follow-up suggests that the implantation of this stent, which is coated with a potent cell-cycle inhibitor, is feasible and safe.

The amount of IH after the implantation of noncoated stents ranges from 19% to 48% of stent volume[3,18,19] by IVUS, and late loss averages 0.8 to 0.9 mm by QCA.[19] Even in nonrestenotic stents that are ≤15 mm long, an average IH

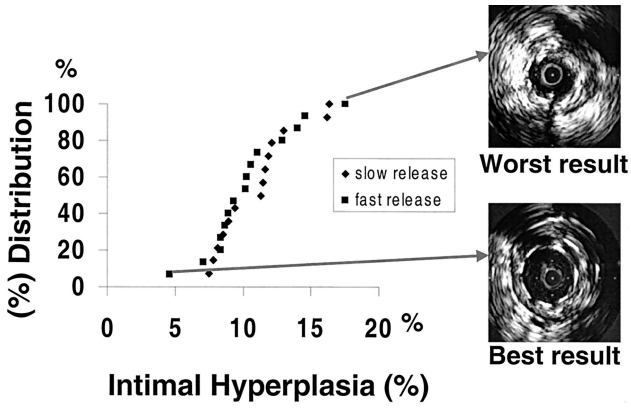

Figure 1. Left, Cumulative distribution curves of percent IH in SR and FR groups. Upper right panel shows follow-up IVUS cross-section with largest amount of IH (17.5%), and lower right panel displays IVUS cross-section with lowest amount of IH (4.6%). In both vessels, a FR stent was implanted (arrows).

TABLE 1. Offline Quantitative Coronary Analysis by Core Laboratory

Parameters	SR Group (n=15)	FR Group (n=15)
Before procedure		
RD, mm	2.98±0.4	2.94±0.3
MLD, mm	1.16±0.3	0.93±0.4
DS, %	62±7	68±14
Lesion length, mm	12.9±1.97	13.1±2.2
Lesion type B1,* %	27	47
Lesion type B2,* %	73	33
After procedure		
RD, mm	3.1±0.4	2.96±0.3
In-lesion MLD, mm	2.74±0.4	2.68±0.3
In-stent MLD, mm	2.94±0.44	2.84±0.3
In-lesion DS, %	11.44±5.5	9.7±5.8
In-stent DS, %	5.09±6.72	4.2±7.4
Follow-up		
RD, mm	2.99±0.4	3.07±0.3
In-lesion MLD, mm	2.6±0.5	2.7±0.4
In-stent MLD, mm	2.9±0.5	2.93±0.3
In-lesion DS, %	14.5±9.1	12.7±8.2
In-stent DS, %	5.04±6.7	4.55±5.7
In-lesion late loss, mm	0.16±0.3	−0.02±0.3
In-stent late loss, mm	0.09±0.3	−0.1±0.3

Values are mean±SD. RD indicates reference diameter; MLD, minimum lumen diameter; and DS, diameter stenosis.

*According to AHA/ACC classification

TABLE 2. Postprocedure and Follow-Up 3D IVUS Measurements by Core Laboratory

	Lumen Volume, mm^3			Stent Volume, mm^3			Neointimal Hyperplasia	
	Post	FUP	*P*	Post	FUP	*P*	Volume, mm^3	Percent
Total	141.6±35	127.8±36	<0.01	141.6±35	142.8±39	NS	15.0±5	10.7±3.0
SR group	152.2±40	137.6±40	<0.01	152.2±40	154.4±44	NS	16.8±6	11.0±3.0
FR group	131.3±31	118.7±30	<0.01	131.3±31	132.0±31	NS	13.3±4	10.4±3.0
P	NS	NS		NS	NS		0.07	NS

Data are mean±SD, unless otherwise indicated. Post indicates postprocedure; FUP, follow-up.
*SR vs. FR.

of 19.7% has been observed by IVUS.[18] Although differences in population and stent design limit scientific comparison with other reports, it is worth noting that the amount of IH detected in the present study (10.7%; essentially zero late loss by QCA) is much lower than previously reported. This is likely due to the cytostatic effect of sirolimus.[10–12,20]

Using the same IVUS methodology, the amount of in-stent IH with radioactive stent implantation varied from 7.4% (6 to 12 μCi radioactive stent) to 16.7% (0.75 to 1.5 μCi).[17] However, neither edge restenosis nor stent thrombosis, both of which have been reported after radiation,[2,3] were observed after the implantation of sirolimus-coated stents (Figure 2).

As a result of their permanent scaffolding action, stents have become an attractive platform for delivering medications locally.[5,21] Although some polymers have been associated with a marked inflammatory reaction,[22] these findings were not observed with the polymers used in the present investigation or in other clinical situations.[13,14] In the present study, similar favorable results were observed with both the FR and SR formulations of the sirolimus-coated stent. Whether one sirolimus coating matrix is superior to the other (SR versus FR) requires further investigation.

Limitations

The study comprises a registry of only 30 patients with 4 months of QCA and 3D IVUS data and 8 months of clinical data. However, considering the absence of late loss by QCA and the virtual absence of IH observed in the present study by 3D IVUS and the well-documented degree of late loss with uncoated stents, these early results are promising. Twelve-month angiographic and IVUS follow-up will be performed in all patients to assess whether this effect is sustained.

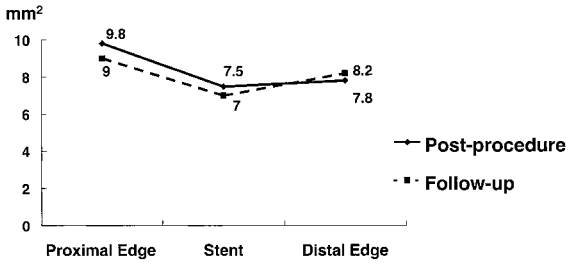

Figure 2. Postprocedure and follow-up mean lumen areas within stent and at 5-mm edge segments (n=30), as assessed by 3D IVUS.

Conclusion

Sirolimus-coated BX Velocity stents seem to be safe and effective in preventing neointimal formation at 4 months after stent implantation in de novo lesions. These seminal findings warrant further confirmation by large, placebo-controlled, multicenter trials.

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