Paclitaxel Coating Reduces In-Stent Intimal Hyperplasia in Human Coronary Arteries

A Serial Volumetric Intravascular Ultrasound Analysis From the ASian Paclitaxel-Eluting Stent Clinical Trial (ASPECT)

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Background—The aim of this study was to use serial volumetric intravascular ultrasound (IVUS) to evaluate the effect of a paclitaxel coating on in-stent intimal hyperplasia (IH).

Methods and Results—Patients were randomized to placebo (bare metal stents) or 1 of 2 doses of paclitaxel (low dose: 1.28 μg/mm^2; high dose: 3.10 μg/mm^2). Complete post-stent implantation and follow-up IVUS were available in 81 patients, including 25 control patients and in 28 receiving a low-dose and 28 receiving a high dose. Volumetric analysis of the stented segment and of both reference segments was performed. Baseline stent measurements and both reference measurements were similar among the groups. With increasing doses, there was a stepwise reduction in IH accumulation within the stented segment (31 ± 22 mm^3 in control, 18 ± 15 mm^3 in low dose, and 13 ± 14 mm^3 in high dose, $P<0.001$). Post hoc analysis showed less IH accumulation when low- and high-dose patients were compared with control ($P=0.009$ and $P<0.001$, respectively), but not when low-dose patients were compared with high-dose patients ($P=0.2$). Focal late malapposition was seen in 1 high-dose patient. With increasing doses, there was no significant change in the reference segments.

Conclusions—Paclitaxel-coated stents are effective in reducing in-stent neointimal tissue proliferation in humans. They are not associated with edge restenosis or significant late malapposition. **(*Circulation*. 2003;107:517-520.)**

Key Words: stents ■ restenosis ■ ultrasonics

The major limitation of coronary stenting is in-stent restenosis (ISR) secondary to intimal hyperplasia (IH).[1] Various treatment modalities, including radiation at the time of stent implantation, have not reduced first-time ISR.[1] However, recent studies of sirolimus-eluting stents have reported a dramatic reduction of first-time ISR.[2,3] The aim of the current study was to use serial volumetric intravascular ultrasound (IVUS) to evaluate the efficacy of paclitaxel coating in inhibiting IH after stenting in humans.

Methods

ASPECT (ASian Paclitaxel-Eluting Stent Clinical Trial) was a three-center, triple-blind, randomized, placebo-controlled trial of paclitaxel-coated stents to reduce ISR. Single de novo lesions in 177 patients were randomized to placebo (bare metal stents) or 1 of 2 doses (low dose: 1.28 μg/mm^2 stent surface area and high dose: 3.10 μg/mm^2; overall dose 54 to 60 μg and 130 to 146 μg, respectively, depending on stent diameter). SupraG stents (Cook Cardiology), which are 316L stainless-steel slotted-tube design, 15 mm in length and stent diameters in 2.5 to 3.5 mm, were used in this study. Preclinical testing using a porcine coronary model showed inhibition of IH at 1 and 6 months with acceptable safety. On the basis of animal studies, doses of 3.10 μg/mm^{2}and 1.28 μg/mm^2 were considered reasonable for study in a human trial. Low- and high-dose stents were coated with pure paclitaxel using a proprietary process. No polymer was used. After the release of paclitaxel, only a bare metal stent remained. Patients were treated with antiplatelet agents for 6 months. The current IVUS analysis was a single center (Asan Medical Center) substudy of ASPECT. Ninety-eight patients were enrolled in this IVUS substudy. All patients gave their written, informed consent. This study was approved by Asan Medical Center Institutional Review Board.

Complete serial (post-stent implantation and 6-month follow-up) IVUS was available in 81 patients, including 25 control, 28 low-dose, and 28 high-dose patients. No differences existed in baseline characteristics when comparing patients in the IVUS substudy versus the total cohort or when comparing paclitaxel-coated stents versus placebo patients in the IVUS substudy (Table 1).

IVUS Imaging and Analysis

IVUS imaging was performed after intracoronary administration of 0.2 mg nitroglycerin by use of a motorized transducer pullback

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TABLE 1. Baseline Characteristics

	High Dose	Low Dose	Placebo
No. of patients	28	28	25
Age, y	58±9	60±9	58±11
Male sex	22 (79)	19 (68)	20 (80)
Diabetes mellitus	2 (7)	5 (18)	5 (16)
Hypercholesterolemia	3 (11)	0 (0)	5 (20)
Hypertension	10 (36)	13 (46)	10 (40)
Current smoking	15 (54)	12 (43)	14 (56)
No. of diseased vessels			
1	17 (61)	20 (71)	18 (72)
2	8 (29)	6 (21)	6 (24)
3	3 (11)	2 (7)	1 (4)
Vessel stented			
Left anterior descending	17 (61)	14 (50)	10 (40)
Right coronary	4 (14)	9 (32)	8 (32)
Left circumflex	6 (21)	4 (14)	7 (28)
Ramus	1 (4)	1 (4)	0 (0)
Lesion classification			
A	20 (71)	20 (71)	16 (64)
B1	7 (25)	8 (29)	8 (32)
B2	1 (4)	0 (0)	1 (4)
C	0 (0)	0 (0)	0 (0)
Ostial lesion	0 (0)	1 (4)	0 (0)
Reference vessel diameter, mm	2.9±0.4	2.9±0.4	2.9±0.4
Pre-stenting minimum lumen diameter, mm	0.6±0.3	0.6±0.3	0.6±0.3
Post-stenting minimum lumen diameter, mm	2.8±0.3	2.8±0.5	2.8±0.4

Data are presented as mean±1SD or n (%).

system (0.5 mm/s) and commercial scanner (SCIMED) consisting of a 30 MHz transducer within 3.2Fr imaging sheath.

Quantitative volumetric IVUS analysis was performed in an independent core laboratory (N.J.W.). With the use of computerized planimetry, stent and reference segments were measured every 1 mm. Reference segment external elastic membrane (EEM), lumen, and plaque and media (P&M=EEM − lumen) areas were measured over a 5-mm length adjacent to stent edge and averaged. Stent, lumen, and IH (stent − lumen) areas were measured every 1 mm within the stented segment; volumes were calculated using Simpson's rule. The minimum lumen area was also measured. These methods have been reported and used previously.[4] Late malapposition was defined as a separation of stent struts from the intimal surface of the arterial wall that was not present postimplantation.[4] The primary endpoint of this analysis was intra-stent IH accumulation at follow-up.

Statistical Analysis

Statistical analysis was performed with Statview 4.5 (SAS Institute). Data are presented as frequencies or mean±1SD. Comparison was performed with a Pearson's χ^2 test, unpaired or paired *t* test, and factorial ANOVA with post hoc comparison using the Bonferroni correction.

Results

IVUS-guided stenting was successfully performed in all patients without additional stenting or any complications. Adjunct balloon angioplasty after IVUS was performed for

TABLE 2. IVUS Measurements

	Placebo	Low Dose	High Dose	*P* by ANOVA
After intervention				
Proximal reference segment				
Mean EEM area, mm^2	15.3±4.5	15.3±5.5	13.3±2.9	0.3
Mean lumen area, mm^2	7.7±2.6	8.0±3.5	6.7±1.8	0.3
Mean P&M area, mm^2	7.6±3.4	7.3±3.3	6.6±1.9	0.6
Stented segment				
Stent volume, mm^3	106±26	105±34	102±29	0.9
Lumen volume, mm^3	106±26	105±34	102±29	0.9
IH volume, mm^3	1±4	0	0	0.3
Minimum lumen area, mm^2	5.7±1.6	5.8±2.1	5.6±1.7	0.9
Distal reference segment				
Mean EEM area, mm^2	12.1±3.8	11.9±4.5	12.0±3.9	0.9
Mean lumen area, mm^2	6.4±2.1	6.7±2.6	6.6±2.2	0.9
Mean P&M area, mm^2	5.7±3.1	5.2±2.7	5.4±2.3	0.9
Follow-up				
Proximal reference segment				
Mean EEM area, mm^2	15.1±3.8	14.7±5.1	13.4±3.5	0.6
Mean lumen area, mm^2	6.5±2.4	7.2±3.9	6.7±2.4	0.8
Mean P&M area, mm^2	7.5±3.1	7.3±2.9	6.7±1.6	0.6
Stented segment				
Stent volume, mm^3	104±25	104±32	102±28	1.0
Lumen volume, mm^3	72±27	85±35	89±27	0.11
IH volume, mm^3	31±22	18±15	13±14	<0.001*
Minimum lumen area, mm^2	3.1±1.5	4.1±2.2	4.5±1.7	0.024†
Distal reference segment				
Mean EEM area, mm^2	11.5±3.7	11.8±4.3	11.7±3.7	1.0
Mean lumen area, mm^2	5.8±2.1	6.2±2.7	6.4±2.6	0.8
Mean P&M area, mm^2	5.7±2.7	5.7±2.3	5.3±1.9	0.9
Serial (after intervention to follow-up) comparison				
Proximal reference segment				
ΔMean EEM area, mm^2	−1.2±2.3	−0.8±1.8	0.2±1.4	0.067‡
ΔMean lumen area, mm^2	−1.2±1.8	−0.8±1.6	0.0±1.3	0.045§
ΔMean P&M area, mm^2	0.0±1.4	0.0±1.7	0.1±1.1	0.9
Stented segment				
ΔStent volume, mm^3	−2±8	−1±11	0±11	0.7
ΔLumen volume, mm^3	−33±28	−20±18	−12±18	0.003‖
ΔIH volume, mm^3	31±22	18±15	13±14	<0.001¶
ΔMinimum lumen area, mm^2	−2.6±1.8	−1.7±1.5	−1.1±1.3	0.002#
Distal reference segment				
ΔMean EEM area, mm^2	−0.6±1.9	−0.1±0.7	−0.3±1.6	0.7
ΔMean lumen area, mm^2	−0.6±1.6	−0.6±1.1	−0.2±1.6	0.7
ΔMean P&M area, mm^2	0.0±1.2	0.4±0.9	0.0±1.0	0.3

Post hoc comparisons.
*P=0.006 placebo vs low dose and P<0.001 placebo vs high dose
†P=0.055 placebo vs low dose and P=0.076 placebo vs high dose
‡P=0.022 placebo vs high dose
§P=0.014 placebo vs high dose
‖P=0.032 placebo vs low dose and P<0.001 placebo vs high dose
¶P=0.009 placebo vs low dose and P<0.001 placebo vs high dose
#P=0.028 placebo vs low dose and P<0.001 placebo vs high dose

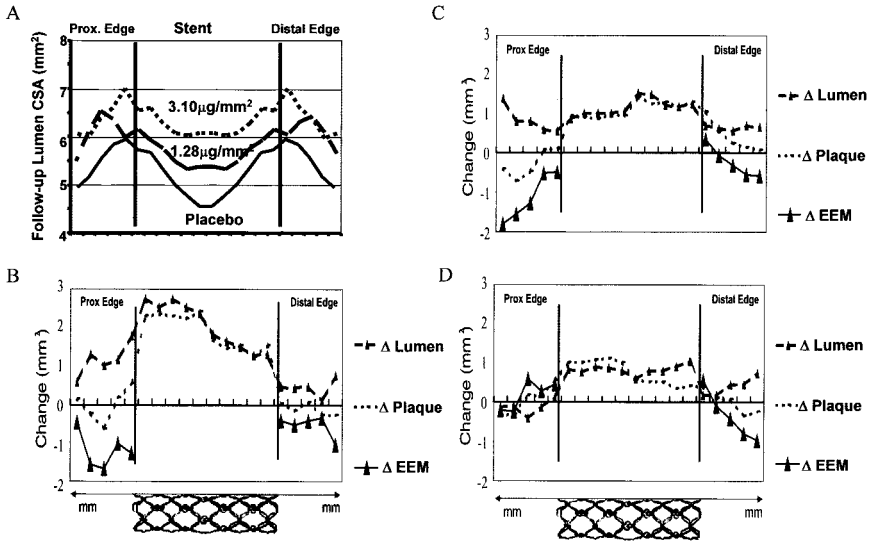

Figure 1. A, Follow-up lumen area for all 3 groups. The serial changes in reference segment external elastic membrane (EEM), plaque, and lumen and in intra-stent lumen and intimal hyperplasia areas are shown in B (placebo), C (low dose), and D (high dose). Measurements were made every 1 mm.

stent optimization in 9 patients (3 patients in each groups); in these patients, IVUS was repeated as the last step in the procedure. Serial IVUS measurements are shown in Table 2. Baseline stent and reference measurements were similar among the 3 groups. Follow-up lumen area and changes (after intervention to follow-up) in reference segment EEM, lumen, and P&M area and intra-stent lumen and IH area in the 3 groups are shown in Figure 1.

In the stented segment of all 3 groups from after implantation to follow-up, there was a decrease in lumen volume and an increase in IH volume ($P<0.0001$ for all comparisons). With increasing doses of paclitaxel, however, there was a stepwise reduction in IH accumulation within the stented segment (31 ± 22 mm^3 in control, 18 ± 15 mm^3 in low-dose, and 13 ± 14 mm^3 in high-dose patients; $P<0.001$). Post hoc analysis showed less IH accumulation when low- and high-dose patients were compared with placebo patients ($P=0.009$ and $P<0.001$, respectively), but not when low-dose patients were compared with high-dose patients ($P=0.2$). Similar findings were seen in the follow-up minimum lumen area. With increasing doses, there were no significant changes in reference segment measurements.

When postintervention and follow-up IVUS studies were compared side-by-side, focal (less than 1 quadrant in circumference and less than 2 mm in length) late malapposition was seen in 1 high-dose patient (Figure 2), but in no low-dose or placebo patients. In this 1 patient, late malapposition was associated with positive remodeling (increase in EEM).

Discussion

The current IVUS study demonstrated that a paclitaxel coating reduces in-stent neointimal tissue proliferation. These data are consistent with the results of previous serial IVUS studies of sirolimus-eluting stents.[2,3] The RAndomized study with the sirolimus-eluting Bx VELocity balloon-expandable stent (RAVEL) trial reported dramatic results of a 0% angiographic restenosis rate in the sirolimus-stent group.[3] The ASPECT trial showed similar findings; angiographic reste-

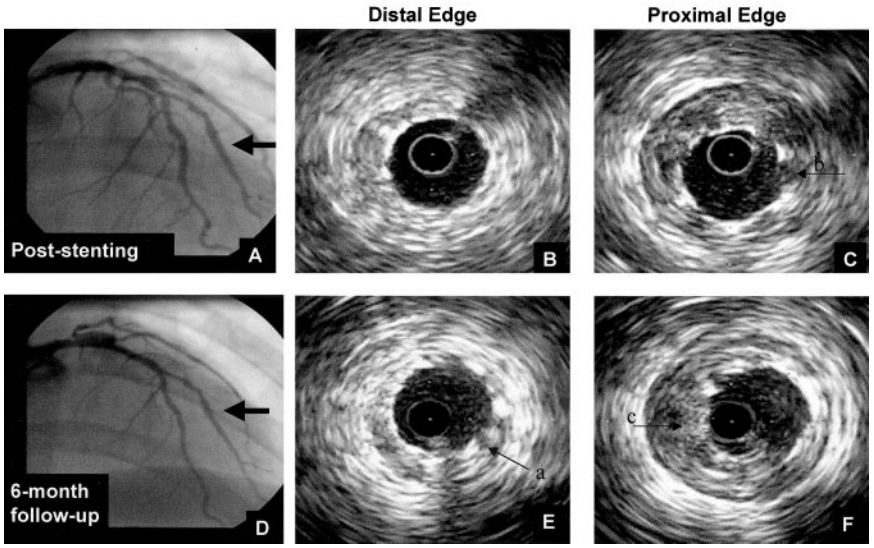

Figure 2. Post-stenting (A, B, and C) and follow-up (D, E, and F) angiographic and IVUS studies in the 1 patient with late malapposition. At the distal edge, there was complete apposition after stenting, but focal late malapposition at follow-up (arrow a). At the proximal edge there was malapposition both after stenting (arrow b) and at follow-up (arrow c). There was no intimal hyperplasia.

nosis was reduced from 27% in the control group to 4% in the high-dose group.

Paclitaxel and sirolimus have been reported to reduce vascular cell proliferation and intimal thickening in models of vascular injury.[5,6] The reported mechanisms of action might also lead to late vessel enlargement (positive remodeling) at the stented segment, similar to intracoronary brachytherapy.[7] Positive remodeling coupled with inhibition of IH can cause late malapposition. Late malapposition must be differentiated from malapposition present at implantation that was only detected at follow-up. The higher overall dose (in the high-dose stent group) might be the cause of the 1 case of late malapposition.[6] The follow-up IVUS substudy of RAVEL showed a 21% incidence of late malcomplete apposition in the sirolimus group.[8] However, there was only 1 case of focal late malapposition in the high dose group in this study. Therefore, it is imperative that IVUS be performed both at implantation and at follow-up, as was done in the current study.

The current study also assessed the impact of paclitaxel on nearby reference segments. Serial IVUS analysis of patients treated as part of brachytherapy protocols identified focal edge lumen loss, termed the "candy-wrapper effect," resulting from a focal increase in neointima at the stent edge.[7] This was not seen in the current study.

Limitations

Serial IVUS study was performed in only a subset of the 177 patients enrolled in ASPECT.

Conclusions

Paclitaxel-coated stent implantation is effective in reducing in-stent neointimal proliferation in humans. It is not associated with significant late malapposition or edge lumen loss.

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