Feasibility, Safety, and Efficacy of a Novel Polymeric Pimecrolimus-Eluting Stent

Traditional Pre-Clinical Safety End Points Failed to Predict 6-Month Clinical Angiographic Results

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Objectives The aim of this study was to determine the safety and efficacy of a novel pimecrolimus-eluting stent in a porcine coronary model and in a phase I clinical trial.

Background Rapamycin- and paclitaxel-eluting stents reduce the need for repeat intervention by limiting neointimal hyperplasia but might cause delayed healing, pre-disposing patients to late stent thrombosis. Because inflammation plays a key role in restenosis, pimecrolimus, an anti-inflammatory drug, might reduce restenosis without adversely affecting re-endothelialization.

Methods We evaluated a novel polymeric pimecrolimus-eluting stent covered with a thin parylene C diffusion barrier in a porcine coronary model and in a phase I human clinical trial. The clinical study was a prospective, nonrandomized, first-in-human hypothesis-generating study that enrolled 15 patients who had a single de novo native coronary stenosis.

Results At 28 days and 3 months in the porcine model, histopathologic indicators predicted safety and biocompatibility when stents coated with polymer only, drug only, and 2 drug-polymer formulations were compared with bare-metal stents (BMS). In the phase I clinical trial, 15 patients had successful implantation of pimecrolimus-eluting stents. By 6 months, no patient suffered death, myocardial infarction, or stent thrombosis. However, the angiographic restenosis (61%), mean late loss (1.44 mm), and repeat target lesion revascularization (53%) were significantly higher than historical BMS controls. Whereas the primary end point was percent volume obstruction, restenosis was so severe that operators performed intravascular ultrasound examination in only 6 patients.

Conclusions Pimecrolimus-eluting stents induced an exaggerated neointimal hyperplasia at 6 months in comparison with historical controls. (J Am Coll Cardiol Intv 2009;2:1017–24) © 2009 by the American College of Cardiology Foundation

First-generation drug-eluting stents (DES) eluting rapamycin or paclitaxel reduce restenosis and the need for repeat target lesion revascularization (TLR) (1,2). Unfortunately, the nonspecific nature of these stent-based therapies likely contributes to delayed healing or incomplete re-endothelialization associated with a small increase in late stent thrombosis (3–7). The ideal DES formulation would limit neointimal formation without delaying healing or endothelialization of the stent.

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Acute and chronic inflammation play a central role in neointimal development, and it has thus been proposed as a target for prevention of restenosis (8,9). Pimecrolimus (Novartis Pharma AG, Basel, Switzerland) is a potent anti-inflammatory compound that binds to macrophilin-12 (FKBP-1) and inhibits the calcium-dependent phosphatase, calcineurin. It is not a rapamycin analog, and its mechanism of action is independent of the mammalian target of rapamycin (mTOR). Pimecrolimus is a derivative of macrolactam ascomycin produced by the bacterium *Streptomyces hygroscopicus var. ascomyceticus.* The compound inhibits T-cell activation by blocking of the transcription of pro-inflammatory cytokines. Pimecrolimus inhibits interleukin-2, interferon gamma (Th1-type), interleukin-4, and interleukin-10 (Th2-type) cytokine synthesis in human T cells at nanomolar concentrations. In addition, pimecrolimus prevents the release of inflammatory cytokines and the mediators from mast cells in vitro after stimulation by antigen/IgE.

The efficacy of stent-based pimecrolimus delivery in a porcine coronary model has been demonstrated for 2 additional and different stent designs coated with different stent-polymer formulations (10,11). These studies demonstrated complete endothelialization, a reduction in neointimal area at 28 days compared with bare-metal stent (BMS) controls, and no histological indicators of delayed healing. These studies supported the hypothesis that stent-based delivery of pimecrolimus inhibits neointimal formation without delayed healing in the porcine coronary model.

The aim of our study was to evaluate the feasibility, safety, and efficacy of a novel pimecrolimus-eluting stent in a porcine coronary model and in a phase I human clinical trial.

Abbreviations and Acronyms

BMS = bare-metal stent(s)

DES = drug-eluting stent(s)

IVUS = intravascular ultrasound

mTOR = mammalian target of rapamycin

PCI = percutaneous coronary intervention

QCA = quantitative coronary angiography

TLR = target lesion revascularization

TVR = target vessel revascularization

Methods

Materials. The components of this novel anti-inflammatory DES are a stainless steel balloon-expandable platform (Duraflex, Avantec Vascular, Sunnyvale, California), the drug pimecrolimus, and a nonbiodegradable polymeric diffusion barrier designed to modulate drug release (parylene C).

The Duraflex BMS, evaluated in a Japanese prospective registry and in the IMPACT (Inhibition with MPA of Coronary Restenosis Trial) (12), received CE Mark approval in 2000 and is commercially available in over 30 countries.

Pimecrolimus in a solvent was sprayed onto the stent at room temperature and then air-dried at 50°C for 10 h. The dose on the stents used in the clinical trial was 400 μg of pimecrolimus/stent. A parylene C diffusion barrier was applied to the drug coating by a chemical vapor deposition method at room temperature. The total thickness of the drug-polymer layer was approximately 3 to 4 μm. The devices were sterilized with ethylene oxide at 32°C.

Drug extraction and quantification by high-performance liquid chromatography confirmed that no degradation of pimecrolimus occurred during the manufacturing process. In vitro pharmacokinetic studies demonstrated release of 15% of the drug at 1 day and 35% at 7 days in a static porcine serum infinite sink.

Retained samples of stents from the same manufacturing lot used in the clinical trial, independently analyzed (Evans Analytical Group, Sunnyvale, California), demonstrated that any trace amounts of contaminants and organic solvents were well below manufacturing standards (13). High-performance liquid chromatography demonstrated 99% pure residual pimecrolimus without oxidative species.

Preclinical studies. The histopathologic specimens from preclinical studies in a porcine coronary model were independently analyzed by a cardiac pathologist. Analysis included all samples from 28-day and 12-week feasibility, safety, efficacy and toxicity overlap implants with a BMS control, 0.2-μm-thick polymer only, drug-only (pimecrolimus 200 μg), and 2 different drug-polymer formulations (pimecrolimus 300 μg with 0.2-μm barrier and pimecrolimus 400 μg with 0.2-μm barrier). Twenty-five porcine hearts with 66 stented arteries (10 pairs of overlapping stents) were implanted with stents with an intended balloon/artery ratio of 1.1/1. Explanted stents were examined from the 28-day study. Scanning electron microscopy was conducted on 9 of 56 vessels with single stents. Eighteen hearts and 37 stented arteries were examined at 90 days. Stented and adjacent nonstented sections were examined with established methodology (14,15).

Phase I clinical trial. The study was approved by the Auckland Ethics Committee, and each patient gave written informed consent before stent implantation. Patients with angina or documented silent ischemia and suitable coronary

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lesions undergoing percutaneous coronary intervention (PCI) were enrolled between March and June 2006. The lesion to be treated was a single de novo native coronary artery stenosis of $\geq$50% and <100% diameter, visually estimated to be in a vessel segment $\geq$3.0 mm and $\leq$3.5 mm in diameter with a maximum length of 14 mm and Thrombolysis In Myocardial Infarction coronary flow $\geq$1. Aorto-ostial lesions, unprotected left main lesions, and lesions within 2 mm of the origin of the left anterior descending or left circumflex were excluded. Patients who had suffered a myocardial infarction with total creatine kinase >3$\times$ normal within the previous 72 h were also excluded.

Clinical trial design and study end points. The clinical trial was a prospective, nonrandomized, consecutive enrollment registry carried out at 2 sites in Auckland, New Zealand. The goal was to evaluate the safety and potential inhibition of neointimal thickening by pimecrolimus eluted from the Avantec Duraflex drug-eluting stent at 6 months through clinical, angiographic, and intravascular ultrasound (IVUS) end points.

The primary end point was percent volume obstruction assessed by IVUS at 6 months. Secondary end points were major adverse cardiac events (MACE) at 1, 6, 9, and 12 months. A MACE was defined as death, Q-wave MI, non–Q-wave MI, and revascularization by surgery or PCI attributed to the target lesion. Additional secondary end points were acute success, TLR, and target vessel revascularization (TVR) at 1, 6, 9, and 12 months. Angiographic end points were binary restenosis and in-stent late lumen loss at 6 months.

Statistical analysis. PRE-CLINICAL STUDY. Normality of data was tested with the Shapiro-Wilk test. Measurements of artery size and percent stenosis were reported as mean $\pm$ SD. Injury score and inflammation are reported as median and interquartile range due to their skewed distribution. Analysis of variance was used to assess differences in stenosis severity and artery measurements in the 5 test groups. The *F* test and post-analysis of variance Tukey Honestly Significant Difference test were used for the pairwise comparisons. Kruskal-Wallis tests were used to assess if there were differences in average injury and inflammation scores across groups.

CLINICAL STUDY. This was a first-in-human pilot study designed to obtain preliminary observations and generate hypotheses for future studies. As such the sample size was not calculated on the basis of an end point hypothesis but to provide information on device efficacy and safety. The mean, SD, and 95% confidence intervals were determined for continuous variables, and results were compared with previously published findings with the BMS Duraflex (12) in similar patient and lesion populations. To assess whether the mean parameters of the current samples were significantly different from means of these parameters from historical controls, 1-sample *t* tests were applied.

Procedure. Stenting was carried out in the standard manner at each center, with either heparin or bivalirudin anticoagulation. The patients were pretreated with aspirin, and those not pretreated with clopidogrel received a 600-mg loading dose at the time of the procedure. Aspirin was administered after the procedure for at least 1 year, and clopidogrel was administered for at least 3 months.

Clinical study management. The pre-clinical specimens were analyzed by the Biomedical Research Foundation of South Texas.

For the clinical trial, the IVUS and quantitative angiographic (quantitative coronary angiography [QCA]) core laboratory was the Stanford Cardiovascular Core Analysis Laboratory, Stanford University, Palo Alto, California. Data management was by Nextrials, San Ramon, California. Study monitoring was conducted by the clinical regulatory unit of Avantec Vascular Corporation. There was an independent Clinical Events Committee.

Results

Pre-clinical studies. Table 1 summarizes the results of vessel histomorphometry at 28 days. Although the mean neointimal area of the 400-μg pimecrolimus-eluting stents (1.50 $\pm$ 0.42 mm^2) was significantly less than bare-metal controls (2.65 $\pm$ 0.66 mm^2) and polymer only (2.17 $\pm$ 0.86 mm^2) stents, vessel areas were also significantly different (7.68 $\pm$

Table 1. Summary of Vessel Histomorphometry for 47 Single Stents at 28 Days in a Porcine Coronary Model

	BMS	Drug Only	Drug 300 μg With Polymer	Drug 400 μg With Polymer	Polymer Only	p Value
Artery (mm^2)	9.93 $\pm$ 0.93	8.93 $\pm$ 1.92	9.91 $\pm$ 2.00	7.68 $\pm$ 1.20	9.46 $\pm$ 1.50	0.04
Lumen (mm^2)	5.20 $\pm$ 0.97	4.75 $\pm$ 1.27	5.05 $\pm$ 1.87	4.52 $\pm$ 0.79	5.30 $\pm$ 1.38	0.49
Neointima (mm^2)	2.65 $\pm$ 0.66	2.19 $\pm$ 1.26	2.60 $\pm$ 0.74	1.50 $\pm$ 0.42	2.17 $\pm$ 0.86	0.06
Area stenosis (%)	33.96 $\pm$ 8.62	30.58 $\pm$ 14.14	35.12 $\pm$ 12.00	25.04 $\pm$ 6.03	29.71 $\pm$ 12.13	0.35
Injury score	0.33 (0.33–1.00)	0.67 (0.00–1.00)	0.67 (0.00–1.33)	0.33 (0.17–0.84)	0.33 (0.00–0.67)	0.84
Inflammation score	1.00 (0.67–1.00)	0.67 (0.33–1.33)	0.33 (0.33–1.00)	0.33 (0.33–0.67)	0.33 (0.00–0.67)	0.24

Values are mean $\pm$ SD or median (interquartile range). All were analyzable.
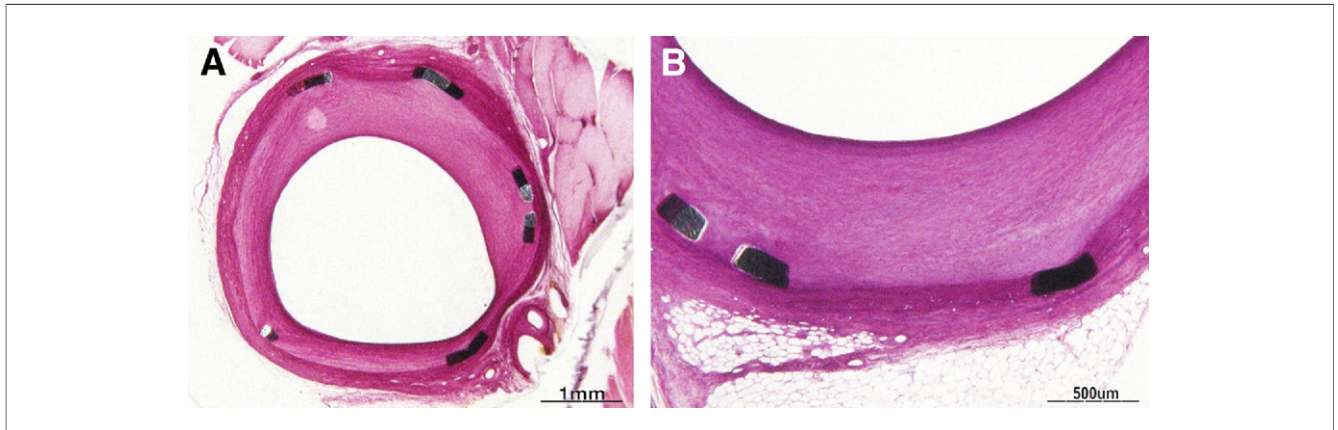
BMS = bare-metal stent(s).

Figure 1. Neointimal Growth and Injury Following a Pimecrolimus Stent Implantation

(A) Low-power section showing neointimal growth and injury in a pimecrolimus stent. More neointima has formed across the top portion of this vessel, where injury is greater and media is absent due to vessel stretch. **(B)** Higher-power section showing a moderate neointimal growth at a region of higher vascular injury.

1.20 mm^2 vs. 9.93 ± 0.93 mm^2) for 400-μg pimecrolimus and BMS controls, respectively. This resulted in a nonstatistically significant percent area stenosis for the 400-μg pimecrolimus-eluting stents (25.0 ± 6.0) compared with BMS (34.0 ± 8.6) and polymer-only (29.7 ± 12.1) stents. The mean neointimal area and percent area stenosis were similar for the polymer-only, 200-μg drug-only, and the 300-μg pimecrolimus-polymer–coated stents as compared with BMS. The vessel injury (range 0.5 to 0.8) and inflammation (range 0.5 to 0.9) scores were similar and low for all study groups. Inflammatory cells consisted of predominantly tissue macrophages and foreign body giant cells. Necrotizing (n = 2) and non-necrotizing (n = 3) granuloma were noted in only 5 of 47 specimens (10.6%) for the single stents (BMS, n = 1; polymer only, n = 3; drug-only, n = 1; 300-μg drug-polymer, n = 0; 400-μg drug-polymer, n = 0). Residual intimal fibrin scores were low and similar for all groups (range 0.1 to 0.2). Endothelialization scores were high (3.0 or complete for all groups). The 9 samples submitted for SEM showed patent lumens with the luminal surface fully covered by mature cobblestone or elongated endothelial cells. Figure 1 shows a representative his-

topathologic image of a porcine coronary artery treated with the pimecrolimus stent at 28 days. A modest amount of neointimal thickening occurred in regions of vascular injury.

Table 2 summarizes the results of vessel histomorphometry at 12 weeks. The mean neointimal area and percent area stenosis were similar for the polymer-only, 200-μg drug-only, and the 300- and 400-μg pimecrolimus-polymer coated stents as compared with BMS. The injury (range 0.1 to 0.4) and inflammation (range 0.1 to 0.2) scores were similar and low for all study groups. Tissue macrophages and occasional multinucleated foreign body giant cells were identified without necrotizing granuloma. Residual intimal fibrin was not detected in any of the study groups (fibrin score 0). Endothelialization scores were similar for all groups (range 2.43 for BMS controls, 3.0 or complete for polymer-only, 200-μg drug, and 400-μg drug-polymer). In a few cases, the pathologist observed artificial sloughing of endothelial cells due to tissue processing, which might have contributed to lower endothelial scores.

Clinical results. Patient demographic data are shown in Table 3, and lesion characteristics are shown in Table 4. These were simple lesions, with 80% classified as American

Table 2. Summary of Histomorphometry for 35 Single Stents at 12 Weeks in a Porcine Coronary Model

	BMS	Drug Only	Drug 300 μg With Polymer	Drug 400 μg With Polymer	Polymer	p Value
Artery (mm^2)	7.17 ± 1.34	7.30 ± 1.01	7.70 ± 1.16	7.26 ± 0.79	7.08 ± 1.03	0.63
Lumen (mm^2)	4.51 ± 0.86	4.66 ± 0.58)	4.77 ± 0.75	4.31 ± 0.61)	4.19 ± 0.57	0.52
Neointima (mm^2)	1.14 ± 0.28	1.11 ± 0.35)	1.18 ± 0.44	1.38 ± 0.43	1.44 ± 0.45	0.45
Area stenosis (%)	20.47 ± 4.35	19.05 ± 5.10	19.57 ± 5.51	24.21 ± 6.89	25.28 ± 6.06	0.21
Injury score	0.00 (0.00–0.33)	0.00 (0.00–0.33)	0.00 (0.00–0.33)	0.33 (0.00–0.67)	0.00 (0.00–0.33)	0.21
Inflammation score	0.00 (0.00–0.33)	0.00 (0.00–0.00)	0.33 (0.00–0.33)	0.33 (0.00–0.33)	0.00 (0.00–0.33)	0.18

Values are mean ± SD or median (interquartile range). All were analyzable.

BMS = bare-metal stent(s).

Table 3. Patient Demographic Data (n = 15)

Age, mean yrs (range)	59 (44–74)
Male	8 (53)
Cigarette smoking	
Current smoker	3 (20)
Former smoker	6 (40)
Never smoked	6 (40)
Dyslipidemia	15 (100)
Hypertension requiring medication	8 (53)
Diabetes mellitus	2 (13)
Family history of coronary artery disease	12 (80)
Previous MI	4 (27)
Worst CCS angina class	
I	3 (20)
II	7 (47)
III	0 (0)
IV	2 (13)
Unstable	3 (20)

Values are n (%) unless otherwise indicated.

CCS = Canadian Cardiovascular Society; MI = myocardial infarction.

Heart Association/American College of Cardiology type A (Table 4). Device success was 100%, with the pimecrolimus-eluting stent being successfully delivered and deployed in all 15 patients. No additional stents were implanted.

In-hospital and 30-day MACE was only a single TLR by PCI. By 6 months there were no myocardial infarctions, stent thromboses, or deaths, but 7 of the 13 (54%) had repeat TVR.

Table 5 shows angiographic findings at baseline and follow-up for those patients who received a pimecrolimus-eluting stent and compares these with patients in the Duraflex

Table 4. Lesion Characteristics (n = 15)

Coronary artery	
Right	6 (40)
Anterior descending	6 (40)
Circumflex	3 (20)
TIMI flow before	
0	0
1	0
2	1 (7)
3	14 (93)
Thrombus present	0
Calcification	
Little/none	12 (80)
Moderate/severe	3 (20)
AHA/ACC lesion type	
A	12 (80)
B1/B2	3 (20)
C	0

Values are n (%).

AHA/ACC = American Heart Association/American College of Cardiology; TIMI = Thrombolysis In Myocardial Infarction.

Table 5. Baseline, Post-Procedure, and Follow-Up Angiographic Results

	Pimecrolimus (n = 15)	BMS (n = 50)	p Value*
Baseline			
Lesion length, mm	6.22 ± 1.93	11.80 ± 3.95	0.001
MLD, mm	1.00 ± 0.48	0.79 ± 0.43	0.14
DS, %	65 ± 15	71.6 ± 15.6	0.14
Reference vessel diameter, mm	2.86 ± 0.55	2.72 ± 0.47	0.38
Post-procedure			
In-lesion MLD, mm	2.37 ± 0.57	2.20 ± 0.37	0.30
In-stent MLD, mm	2.76 ± 0.43	2.56 ± 0.40	0.12
In-lesion DS, mm	20.4 ± 15.4	19.5 ± 14.0	0.84
In-stent DS, mm	7.1 ± 13.6	7.9 ± 11.2	0.84

	Pimecrolimus (n = 13)	BMS (n = 50)	p Value*
6-month follow-up			
In-lesion MLD, mm	1.23 ± 0.73	1.66 ± 0.59	0.06
In-stent MLD, mm	1.33 ± 0.73	1.72 ± 0.65	0.08
In-lesion DS, %	57.2 ± 22.2	40.9 ± 19.0	0.02
In-stent DS, %	53.9 ± 22.0	39.0 ± 20.8	0.03
In-lesion late loss, mm	1.12 ± 0.90	0.91 ± 0.49	0.42
In-stent late loss, mm	1.44 ± 0.89	0.85 ± 0.55	0.03
In-lesion binary restenosis, mean	61.5	26.5	na
In-stent binary restenosis, mean	53.8	26.5	na

Values are mean ± SD or %. Baseline, post-procedure, and follow-up angiographic results for the patients who received a pimecrolimus-eluting stent compared with historical bare-metal stent (BMS) controls from the IMPACT trial (12). *One-sample *t* test compared with the expected mean from historical control.

DS = diameter stenosis; MLD = minimum lumen diameter.

BMS control arm of the Impact trial. (12) One patient declined angiographic follow-up, and another was lost to follow-up. Although patients receiving the pimecrolimus-eluting stent had shorter lesions in larger vessels than historical BMS controls, outcomes were significantly worse (Table 5). At angiographic follow-up, the in-segment restenosis rate of 61.5% and the in-stent late loss of 1.44 mm were significantly ($p < 0.01$ and $p < 0.05$) greater than BMS controls (26.5%, 0.91 mm, respectively).

Angiographic frames before and after stenting and at follow-up for the 8 patients with restenosis are shown in Figure 2.

The IVUS results (Table 6) are biased toward those patients with less severe restenosis, because IVUS recordings were made in only 6 patients because the operators were unwilling to make IVUS recordings in patients with severe restenosis.

Discussion

The main findings of the pre-clinical porcine study and the phase I first-in-human trial of a novel pimecrolimus-eluting stent are that pre-clinical testing suggested pimecrolimus stents were safe but did not predict the exaggerated neoin-
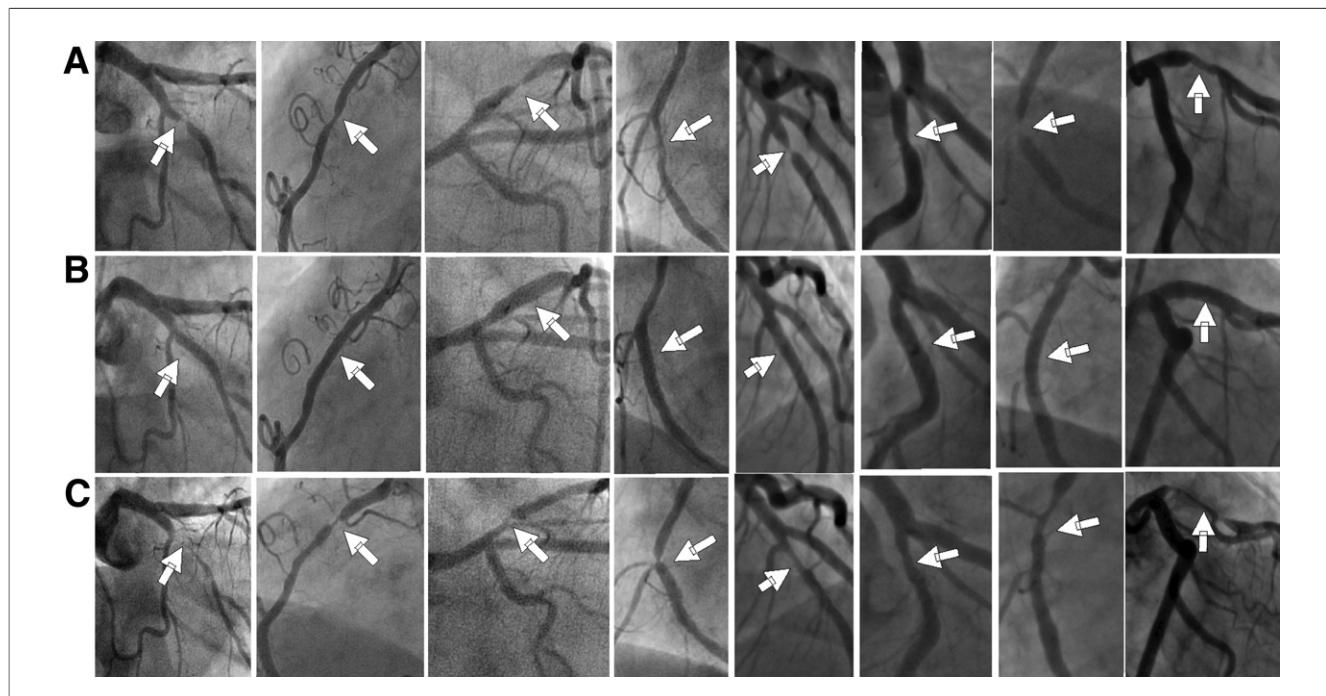
Figure 2. Cine Frames From the 8 Patients Who Had Restenosis by 6 Months

(A) Before stenting, **(B)** after stenting, and **(C)** at follow-up.

timal response seen in patients. Nothing in the pre-clinical study suggested efficacy. In fact there was no apparent reduction in inflammation evident from pre-clinical evaluation, a finding that might have predicted the lack of efficacy. Interestingly, the drug is only approved for topical use, and little is known about its application in the coronary artery. Although this drug has efficacy topically, it might not

have similar efficacy in human coronary arteries. Alternatively, the hypothesis that inflammation is an important mechanism of restenosis might be incorrect, and yet another possibility is that the drug dose was incorrect.

Endothelialization in the juvenile porcine model occurs rapidly and is usually completely different from man. Previous pre-clinical studies showed similar endothelialization between Cypher and BMS (15), yet it did not predict the findings in man (16).

In the clinical trial, neointimal formation was greater with the 400-μg pimecrolimus-eluting polymeric stent than in historical BMS controls (Table 5). The in-stent late loss of 1.44 mm and the angiographic binary restenosis of 61.5% were significantly higher than with historical control patients (0.85 mm and 26.5%, respectively). Target vessel revascularization and TLR were more common (63%) than in control patients (12%).

It is not readily apparent why the pimecrolimus-eluting stent had outcomes that were worse than historical BMS controls (Table 5). Although the pre-clinical studies might not have identified efficacy, they did not identify the exaggerated neointimal response. In general, animal models are reported to predict human responses, but results of this trial confirm that clinical efficacy and safety can only be proven in humans (17,18).

The GENESIS (Randomized, Multicenter Study of the Pimecrolimus-Eluting and Pimecrolimus/Paclitaxel-Eluting Coronary Stent System in Patients with De Novo

Table 6. IVUS Findings After Pimecrolimus Stent Implantation and at Follow-Up

IVUS Analysis	Post-Stent	6-Month
Change in in-stent minimum lumen area, mm² (n = 8)	7.6 ± 1.9	3.8 ± 2.7
Neointimal volume index, mm³/mm (n = 6)		3.4 ± 1.4
Percent neointimal volume (NIH volume/ stent volume), % (n = 6)		39.8 ± 16.6
Vessel volume index	15.6 ± 3.4	15 ± 3.9
Plaque volume index	6.8 ± 3.2	6.4 ± 3.3
Lumen volume index	9.5 ± 1.7	5.7 ± 2.9
Vessel volume index	16.8 ± 4.1	15.2 ± 4.8
Plaque volume index	8.4 ± 4.0	9.3 ± 5.7
Lumen volume index	10.6 ± 4.9	8.5 ± 5.8
Vessel volume index	12.9 ± 5.0	11.2 ± 4.3
Plaque volume index	4.5 ± 3.0	5.3 ± 3.2
Lumen volume index	8.4 ± 2.4	5.9 ± 1.3

Values are mean ± SD. *One-sample *t* test compared with the expected mean of the historical control.

IVUS = intravascular ultrasound; NIH = in-stent neointimal hyperplasia.

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Restenosis After a Pimecrolimus Stent

Lesions of the Native Coronary Arteries) trial (19) that employed pimecrolimus—but released from a bioabsorbable polymer in reservoirs on a different stent platform—had clinical results that were remarkably similar to those from our trial (Table 7). In pre-clinical porcine studies for the GENESIS trial, pimecrolimus released from this platform seemed safe and efficacious (11). The GENESIS trial, terminated early, randomized 249 patients to receive a reservoir stent (Conor Medical, Menlo Park, California) releasing pimecrolimus alone, pimecrolimus plus paclitaxel, or paclitaxel alone. Results for patients in the pimecrolimus arm were remarkably similar to those in our trial, with in-stent late loss in the order of 1.4 mm and with more than one-half the patients suffering restenosis (Table 7). More than one-half of our patients and more than one-third of patients receiving the pimecrolimus-only stent in the GENESIS trial had TVR. Those GENESIS trial patients receiving stents with co-elution of a smaller dose of pimecrolimus in addition to paclitaxel had less late loss, restenosis, and TLR than pimecrolimus alone but more than those patients receiving stents that released paclitaxel alone. Pre-clinical porcine studies had failed to predict the exaggerated intimal hyperplastic response, as in our study. Pimecrolimus is the likely cause of the adverse outcomes, because it is the common factor in the 2 trials that employed different stent platforms and polymers.

In a third pre-clinical study (10), metal stents of a different design eluting different doses of pimecrolimus from an absorbable polymer (Biotronik, Berlin, Germany) seemed safe and efficacious. A clinical trial using this pimecrolimus-eluting stent has completed enrollment, and we await the results.

The release of pimecrolimus from our trial stent was controlled by a barrier layer of Parylene C applied over the drug-coated stainless steel stent. Parylene C has been widely used for over 10 years on medical implants such as pacemakers, implantable defibrillators, and pacing wires. It is a component of coatings on a number of DES, including the Cypher sirolimus-eluting stent (Johnson and Johnson, Miami, Florida), and on the PLA-Biolimus A9-eluting stents (Biosensors International, Inc., Singapore) (20).

Agents aimed at inhibiting coronary restenosis by targeting the inflammatory response after PCI, although prom-

ising in pre-clinical studies, have produced disappointing and at best mixed clinical results (20–25). The pre-clinical and clinical outcomes with systemic as well as stent-based immunosuppressive therapies provide an intriguing analogy to the dichotomous data with the pimecrolimus-eluting stent (21–24).

The vascular pharmacodynamics of a stent-based therapy depend on potential cell-specific responses to a particular compound influenced by the anatomical substrate and phenotypic expression of cellular components integral to the biological effects of the drug.

In pre-clinical models, safety and efficacy are determined in normal animal coronary arteries with a homogenous smooth muscle cell population. Atherosclerotic plaque-derived smooth muscle cells have distinct phenotypes in comparison with medial-derived smooth muscle cells (25). Furthermore, the anatomical substrate as well as smooth muscle cell phenotype can be variable, depending on the type of atherosclerotic plaque (lipid-rich, fibrotic, calcific) (26).

In human clinical trials, polymeric slow-release rapamycin-eluting stents consistently demonstrate a 90% reduction in neointimal hyperplasia in comparison with BMS (1). Others have demonstrated that the abundance of FKBP-12, an intracellular receptor for sirolimus integral to binding with mTOR to form the biologically active complex, varies with smooth cell phenotype and is upregulated by vascular injury (27). Normal medial smooth muscle cells have a low abundance of FKBP-12 in comparison with plaque-derived and neointimal smooth muscle cells. Together these data support the concept that the biological effects of polymeric slow-release sirolimus-eluting stents depend in part on the arterial substrate and perhaps smooth muscle cell phenotype.

Our data suggest, given the proven biocompatibility of the stent and polymer, a possible species or vascular substrate-dependent response to pimecrolimus resulting in induction rather than inhibition of neointimal formation in patients with focal de novo atherosclerotic lesions. Further in vitro and in vivo research might help to elucidate potential biological mechanisms for the exaggerated neointimal response observed in this phase I clinical trial with pimecrolimus-eluting stents.

Study limitations. The porcine model creates vascular injury, and the method of assessment of the injury and its consequence has limitations.

Conclusions

In this phase I clinical trial, pimecrolimus-eluting stents induced an exaggerated intimal hyperplasia at 6 months in comparison with historical controls. Traditional pre-clinical studies predicted correctly the lack of efficacy but did not predict the exaggerated neointimal response. The under-

Table 7. 6-Month Angiographic Follow-Up Results for Patients in the GENESIS Trial			
	Paclitaxel (n = 49)	Paclitaxel and Pimecrolimus (n = 97)	Pimecrolimus (n = 100)
Late loss in stent, mm	0.58 ± 0.58	0.96 ± 0.73	1.4 ± 0.67
Binary restenosis in-lesion, %	7.1	24.2	51.6
Target vessel revascularization, %	2	14.4	35.5

Six-month angiographic follow-up results for patients in the GENESIS trial (18) receiving reservoir stents that eluted paclitaxel alone, paclitaxel and pimecrolimus, and pimecrolimus alone.

standing, development, and validation of novel in vitro and in vivo pre-clinical models are imperative to enable future innovation of stent-based therapies for the prevention of restenosis.

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