Clinical Investigations

Systemic Nanoparticle Paclitaxel (*nab*-Paclitaxel) for In-stent Restenosis I (SNAPIST-I): A First-in-Human Safety and Dose-finding Study

JAMES MARGOLIS, M.D., JOHN McDONALD, M.B., M.R.C.P.,* RICHARD HEUSER, M.D.,† PETER KLINKE, M.D.,* RON WAKSMAN, M.D.,‡ RENU VIRMANI, M.D.,§ NEIL DESAI, PH.D.,¶ DAVID HILTON, M.D.*

Miami International Cardiology Consultants, Miami, Florida; *Victoria Heart Institute Foundation, Royal Jubilee Hospital, Victoria, British Columbia, Canada; †St. Joseph's Hospital, Phoenix, Arizona; ‡Washington Hospital Center, Washington, DC; §CVPPath, International Registry of Pathology, Gaithersburg, Maryland, and ¶Abraxis BioScience, Inc., Los Angeles, California

Summary

Background: Paclitaxel-eluting stents inhibit restenosis; however, this technology has drawbacks (e.g., stent thrombosis, requirement for long-term antiplatelet therapy, and cost—particularly for patients with multivessel disease). Systemic treatment with a novel 130-nm, albumin-bound particle form of paclitaxel (*nab*-paclitaxel) has been shown to reduce restenosis in animals.

Hypothesis: This study was designed to establish the safety and optimal dose of systemic *nab*-paclitaxel for reducing in-stent restenosis in humans. If well tolerated, systemic *nab*-paclitaxel may be used with any available bare-metal stent and at potentially lower cost than drug-eluting stents.

Methods: Patients received *nab*-paclitaxel 10, 30, 70, or 100 mg/m² intravenously after stenting of a single *de novo* lesion ≥3 mm in diameter. Study endpoints included safety and major adverse cardiac events (MACE) at 2 and 6 months.

Results: Data were obtained for all 23 enrolled patients (mean age 66 ± 10 years, 74% men, 26% with diabetes). No significant adverse events (AE) were attributable to *nab*-paclitaxel at 10 or 30 mg/m². Moderate neutropenia,

moderate sensory neuropathy, and mild to moderate, reversible alopecia occurred only at doses of 70 and 100 mg/m²; therefore, doses of 70 mg/m² or higher were considered unacceptable in this patient population. No MACE were reported at 2 months. At 6 months, 4 target lesion revascularizations (TLR) for restenoses were reported (2 each in the 10- and 100-mg/m²-dose groups).

Conclusions: Systemic *nab*-paclitaxel was well tolerated at doses below 70 mg/m² in this group of patients; no unexpected AE were noted. Additional studies are under way to explore intravenous and intracoronary administration of *nab*-paclitaxel.

Key words: drug-eluting stent, albumin-bound paclitaxel, percutaneous coronary intervention, systemic therapy

Clin. Cardiol. 2007; 30: 165–170.

© 2007 Wiley Periodicals, Inc.

Introduction

Drug-eluting stents have reduced the incidence of restenosis in bare-metal stents. These devices demand a complex physical chemistry between the stent platform, polymer carrier, and selected drug. Clinical efficacy and safety data have been accumulating for paclitaxel-eluting stents.^{1–4} Although the results are encouraging, this technology may have drawbacks, including limitation to certain stent platforms, localized aneurysms, late thrombosis, “late catch-up” phenomena, geographic miss, and cost, particularly for multivessel disease. Drug-eluting stents have been approved for marketing in many countries, but use of these devices is limited, especially outside the United States, owing to cost, reimbursement issues, and the need for long-term antiplatelet therapy.

Address for reprints:

David Hilton, M.D.

Victoria Heart Institute Foundation

200-1900 Richmond Avenue

Victoria, British Columbia

V8R 4R2, Canada

e-mail: dhilton@westheart.net

Received: 18 August 2006

Accepted with revision: 20 November 2006

Published online in Wiley InterScience

(www.interscience.wiley.com).

DOI:10.1002/clc.20066

© 2007 Wiley Periodicals, Inc.

Albumin-bound *nab*-paclitaxel (ABI-007 [Abraxane], Abraxis BioScience, Inc., Los Angeles, California), a 130-nm, solvent-free paclitaxel, is approved in the United States and Canada for the treatment of metastatic breast cancer, with a tumor response rate superior to that of solvent-based paclitaxel and an established safety profile.⁵ The nanotechnology used to create *nab*-paclitaxel allows receptor-mediated uptake of paclitaxel into endothelial cells through gp60 receptors and activated caveolin-1.⁶ Because *nab*-paclitaxel contains no solvents or ethanol, the risk of hypersensitivity reactions is reduced, allowing higher doses than those approved for paclitaxel.^{7,8} The safety and efficacy of *nab*-paclitaxel have been demonstrated in patients with various cancers using doses of 100–375 mg/m².^{5,9–11}

Systemic *nab*-paclitaxel is an alternative delivery strategy that could be used with any currently available, bare-metal stent to inhibit restenosis, potentially at a lower cost. This study was designed to establish the safety and optimal dosing of intravenous *nab*-paclitaxel to reduce in-stent restenosis in *de novo* native coronary artery lesions.

Methods

This study was approved by local institutional review boards and conducted in compliance with Good Clinical Practice, International Conference on Harmonisation (ICH) guidelines, and the Declaration of Helsinki. All patients gave their written informed consents before any study-related procedures were done.

Study Design/Patient Population

The Systemic Nanoparticle Paclitaxel for In-STent Restenosis (SNAPIST-I) study is a prospective, open-label, randomized, multicenter, safety study in patients aged ≥ 18 with angina (Canadian Cardiovascular Society Class I–IV) and evidence of ischemia, but not infarction, left ventricular ejection fraction $\geq 30\%$, and requiring treatment of *de novo* lesions in a single coronary artery (diameter ≥ 3.0 mm, lesion length ≤ 18 mm) with intravascular ultrasound-guided, bare-metal stent placement.

Patients were excluded if they had unprotected left main stem disease ($>50\%$ stenosis), ostial target lesions, saphenous vein or internal mammary graft lesions, in-stent restenotic lesions or prior stent placement within the past 3 months or within 5 mm of the target lesion, angiographic evidence of thrombus, a totally occluded vessel, impaired renal function, recent myocardial infarction (MI), active peptic ulcers or upper gastrointestinal bleeding, peripheral neuropathy (Grade ≥ 1), or were receiving immunosuppressive drugs. Bifurcation lesions were allowed if no side branch >2.0 mm was lost during the procedure. Patients were randomized after successful, uncomplicated completion of the procedure, and only after obtaining a minimum luminal diameter (MLD) of

≥ 3.0 mm or a minimum luminal area of ≥ 7.0 mm² by intravascular ultrasound.

Patients received a single intravenous infusion of *nab*-paclitaxel 10, 30, 70, or 100 mg/m² (10 mg/m²/min) within 30 min of stent deployment. Hematologic evaluation was conducted at 1, 2, and 3 weeks post procedure. Major adverse cardiac events (MACE) were evaluated at 2 and 6 months. All patients received aspirin 325 mg and clopidogrel 300 mg before the procedure, followed by aspirin 81 mg and clopidogrel 75 mg for 6 months. Heparin (or equivalent) was administered during the procedure.

Endpoints

Primary endpoints were the safety of *nab*-paclitaxel, including the incidences of adverse events (AE) and serious adverse events (SAE) throughout the study, and MACE at 2 and 6 months post procedure. Secondary endpoints were MACE and angiographic evaluation of restenosis at 6 months.

Adverse Events

Patients were observed for 4 h post infusion to detect immediate AE (e.g., hypersensitivity). AE that occurred between stent implantation and the 6-month follow-up were graded¹² and recorded. Patients were monitored for MACE, including death, MI, coronary artery bypass graft (CABG), target lesion/vessel revascularization, thrombosis, and bleeding, during the 6-month study period.

Angiography

Quantitative coronary angiography was performed at baseline and 6-month follow-up to assess late lumen loss and binary restenosis. In-segment analysis included areas 5 mm proximal and 5 mm distal to the stent margins. Cardialysis BV (Rotterdam, the Netherlands) performed the angiographic analysis and remained blinded to treatment assignments.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ SD; categorical data were expressed as percentages. Groups of five to seven patients were sufficient to establish doses for future studies based on safety data. Between-group statistical analyses of efficacy were not performed owing to the small sample size.

Results

Patients

Twenty-three patients were enrolled in the study at three sites from October 2001 to June 2003. Baseline characteristics varied slightly between groups but were typical for this patient population (Table 1).

Safety

Safety data were obtained for all patients. No procedure-related AE occurred during post procedure observation. The only SAE occurred at 70 mg/m²; one patient developed a skin infection (reported as possibly drug related) >2 months post procedure, which lasted 5 days and resolved without sequelae. The patient required hospitalization, thereby classifying the episode as an SAE. Three weeks after stent deployment, the patient's ANC and white blood cell count were normal, suggesting that this event was not drug related.

No neutropenia or leukopenia was reported at 10 mg/m²; neutropenia and leukopenia were mild at 30 mg/m² and moderate at 70 and 100 mg/m² (Table 2). Mild-to-moderate anemia was observed at all doses. None of these abnormalities were manifested clinically, and patients recovered spontaneously within a 3-week follow-up.

In general, the number of nonhematologic AE (Table 2) increased with escalating doses (data not shown). All but one of these events were mild to moderate and required no intervention. A Grade 3 event (pruritus, possibly treatment related) occurred in one patient (70-mg/m² group) on the day of the procedure but resolved without medication or sequelae. Reversible, mild-to-moderate alopecia was noted in four patients each in the 70- and 100-mg/m² groups.

MACE

No MACE were reported during the first 2 months (Table 3). One patient in the 100-mg/m² group presented with a nonQ-wave MI at 4 months, resulting in target lesion revascularization (TLR). At 6 months, three additional, angiographically driven TLRs were reported (two at 10 mg/m², one at 100 mg/m²). No MACE were reported in the 30- or 70-mg/m² group at 6-month

TABLE 1 Baseline clinical characteristics

Characteristic	<i>nab</i> -Paclitaxel dose (mg/m ²)				All patients (N = 23)
	10 (n = 7)	30 (n = 5)	70 (n = 6)	100 (n = 5)	
Mean age, years	62.3 ± 7.3	64.4 ± 12.9	71.5 ± 10.0	65.6 ± 11.0	65.9 ± 10.1
Sex, male	6 (86)	3 (60)	No. (%) of Patients 4 (67)		17 (74)
Diabetes					
Total	1 (14)	1 (20)	2 (33)	2 (40)	6 (26)
Insulin-dependent	0	0	2 (33)	1 (20)	3 (13)
Noninsulin-dependent	1 (14)	1 (20)	0	1 (20)	3 (13)
Smoking status					
Current smoker	0	0	0	0	0
Never smoked	3 (43)	2 (40)	3 (50)	2 (40)	10 (43)
Exsmoker	4 (57)	3 (60)	3 (50)	3 (60)	13 (57)
Hypertension	6 (86)	4 (80)	3 (50)	4 (80)	17 (74)
Hypercholesterolemia (>6.5 mmol/L)	4 (57)	3 (60)	5 (83)	5 (100)	17 (74)
Peripheral vascular disease	1 (14)	0	0	0	1 (4)
Stroke	1 (14)	0	0	1 (20)	2 (9)
Prior MI					
Total	2 (29)	2 (40)	2 (33)	0	6 (26)
NonQ-Wave	1 (14)	2 (40)	2 (33)	0	5 (22)
Q-Wave	1 (14)	0	0	0	1 (4)
Prior PCI	2 (29)	1 (20)	3 (50)	2 (40)	8 (35)
Prior CABG	1 (14)	1 (20)	2 (33)	1 (20)	5 (22)
CCS Class (n = 19)					
I	0	0	1 (20)	0	1 (5)
II	3 (75)	4 (80)	2 (40)	3 (60)	12 (63)
III	1 (25)	0	2 (40)	2 (40)	5 (26)
IV	0	1 (20)	0	0	1 (5)
Unstable angina	—	—	1 (20)*	—	1 (5)
Silent ischemia	3 (60) [†]	0	0	0	3 (13)

MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society.

* Braunwald Classification: severity 2, circumstance B.

[†] On the basis of stress test.

TABLE 2 Number (%) of patients with treatment-related toxicities/adverse events*

NCI CTC term	<i>nab</i> -Paclitaxel dose (mg/m ²)								
	All patients (N = 23)	10 (n = 7)	30 (n = 5)		70 (n = 6)			100 (n = 5)	
	All grades	Grade 1	Grade 1	Grade 2	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2
Hematologic									
Anemia	12 (52)	2 (29)	3 (60)	0	4 (67)	0	0	2 (40)	1 (20)
Leukopenia	9 (39)	0	2 (40)	0	3 (50)	1 (17)	0	2 (40)	1 (20)
Neutropenia	4 (17)	0	1 (20)	0	1 (17)	1 (17)	0	0	1 (20)
Thrombocytopenia	2 (9)	1 (14)	0	0	1 (17)	0	0	0	0
Nonhematologic									
Alopecia	8 (35)	0	0	0	0	4 (67)	0	3 (60)	1 (20)
Fatigue	4 (17)	1 (14)	0	0	0	0	0	1 (20)	2 (40)
Diarrhea	3 (13)	0	1 (20)	0	1 (17)	0	0	1 (20)	0
Rash/desquamation	2 (9)	0	0	1 (20)	0	0	0	1 (20)	0
Nausea	1 (4)	1 (14)	0	0	0	0	0	0	0
Vomiting	1 (4)	1 (14)	0	0	0	0	0	0	0
Pruritus	1 (4)	0	0	0	0	0	1 (17)	0	0
Skin infection [†]	1 (4)	0	0	0	0	0	1 (17)	0	0
Hypophosphatemia	1 (4)	0	0	0	0	0	0	1 (20)	0
Blurred vision	1 (4)	0	0	0	0	0	0	1 (20)	0
Sensory neuropathy	1 (4)	0	0	0	0	0	0	0	1 (20)

Note: No Grade 4 toxicities occurred.

* Hematologic toxicities were based on laboratory test values; nonhematologic events were based on adverse event reports.

[†] Considered possibly related to treatment.

TABLE 3 Major adverse cardiac events (MACE)

MACE	<i>nab</i> -Paclitaxel dose (mg/m ²)				All patients (N = 23)
	10 (n = 7)	30 (n = 5)	70 (n = 6)	100 (n = 5)	
Overall MACE at 2 months, no. of patients	0	0	0	0	0
Mean 6-month follow-up, months	6.2 ± 0.3	6.1 ± 0.2	6.1 ± 0.4	6.5 ± 0.5	6.2 ± 0.4
Overall MACE at 6 months, no. (%) of patients	2 (29)	0	0	2 (40)	4 (17)
Death	0	0	0	0	0
Myocardial infarction					
Q-wave	0	0	0	0	0
NonQ-wave*	0	0	0	1 (20)	1 (4)
Coronary artery bypass graft	0	0	0	0	0
Target lesion revascularization [†]	2 (29)	0	0	2 (40)	4 (17)
Target vessel revascularization	2 (29)	0	0	2 (40)	4 (17)
Stent/vessel thrombotic occlusion	0	0	0	0	0
Major bleeding	0	0	0	0	0

* Occurred at 4 months.

[†] Only one patient in the 100-mg/m² dose group with nonQ-wave myocardial infarction had a clinically driven target lesion revascularization.

follow-up. No on-study deaths or CABG procedures were reported.

Angiography

Baseline and postintervention angiographic characteristics were similar for all dose groups (Tables 4 and 5). The mean reference vessel diameter was 3.02 ±

0.67 mm, and the mean lesion length was 10.53 ± 4.30 mm. Mean MLDs before and after the procedure were 1.20 ± 0.38 and 2.88 ± 0.59 mm, respectively, resulting in an in-stent absolute short-term gain of 1.68 ± 0.42 mm. Six-month angiographic analysis (Table 5) was available for 22 patients (96%). No cases of binary restenosis occurred at 30 or 70 mg/m².

TABLE 4 Baseline angiographic characteristics

Characteristic	<i>nab</i> -Paclitaxel dose (mg/m ²)				All patients (N = 23)
	10 (n = 7)	30 (n = 5)	70 (n = 6)	100 (n = 5)	
Target lesion location, no. of patients					
LAD	5	3	2	3	13
RCA	1	2	4	2	9
Circumflex	1	0	0	0	1
Reference vessel diameter, mm	2.98 ± 0.73	3.06 ± 0.36	3.03 ± 0.74	3.03 ± 0.90	3.02 ± 0.67
Lesion length, mm	11.24 ± 5.11	11.84 ± 5.43	9.52 ± 3.53	9.43 ± 3.38	10.53 ± 4.30
Stent length (postprocedure), mm	12.75 ± 4.03	13.83 ± 2.49	10.34 ± 3.58	12.08 ± 1.84	12.21 ± 3.28

LAD = Left anterior descending artery; RCA = right coronary artery.

TABLE 5 Angiographic outcomes at 6-month follow-up

Characteristic	<i>nab</i> -Paclitaxel dose (mg/m ²)				All patients (N = 23)
	10 (n = 7)	30 (n = 5)	70 (n = 6)	100 (n = 5)	
No. of patients at 6-month angiographic follow-up	7	5	6	4	22
Late lumen loss, mm					
In-stent	1.28 ± 0.80	1.02 ± 0.41	0.74 ± 0.36	0.66 ± 1.28	0.96 ± 0.74
In-segment	0.91 ± 0.77	0.46 ± 0.16	0.30 ± 0.12	0.55 ± 0.43	0.58 ± 0.52
Angiographic binary restenosis, % (n/n)					
In-stent	28.6 (2/7)	0 (0/5)	0 (0/6)	50.0 (2/4)	18.2 (4/22)
In-segment	28.6 (2/7)	0 (0/5)	0 (0/6)	50.0 (2/4)	18.2 (4/22)

Binary restenosis in the 10- and 100-mg/m² dose groups occurred in two of seven and two of four patients, respectively.

Discussion

This study investigated the safety and dose ranging of systemic nanoparticle paclitaxel in patients with *de novo* coronary lesions. Limitations of this study included a small sample size and between-group differences in baseline characteristics. Most of the side effects that occurred at lower doses were mild to moderate in severity and resolved without intervention. Mild-to-moderate alopecia only occurred at the higher dose levels. Although reversible, alopecia was considered an unacceptable side effect in this patient population.

In comparison to published studies with oral rapamycin,^{13–16} drug-related AE in SNAPIST-I were relatively mild and less frequent.

MACE in this study were driven primarily by TLR, with no deaths, MIs, or CABG procedures reported. No MACE occurred in the 30- or 70-mg/m² dose group, but there were 2/7 (29%) and 2/4 (50%) MACE in the 10- and 100-mg/m² dose groups, respectively. The

patient population in this study was small; however, for reference, the overall MACE was 22% in the oral rapamycin (ORBIT) study¹⁵ and 0% in the drug-eluting stent arm of the TAXUS I study.¹

In-segment late losses (Table 5) in the 30- and 70-mg/m² groups (0.46 and 0.30 mm, respectively) were slightly higher than those seen with paclitaxel-eluting stents (0.23 mm)⁴ but lower than those seen with oral rapamycin (0.64 mm).¹⁵ However, the sample size was too small to determine efficacy, and this will be investigated in larger studies. A formal dose-response analysis was not done because of the small sample size, but there appeared to be a trend toward decreasing late loss with increasing dose (Table 5). The 10-mg/m² dose appeared to be ineffective, and the 100-mg/m² dose resulted in unacceptable side effects.

If systemic delivery of *nab*-paclitaxel proves effective for preventing or reducing restenosis, cost savings over drug-eluting stents could be considerable, especially for treatment of multiple lesions. Drug-eluting stents often require lifelong antiplatelet therapy due to risk of thrombosis, which adds significant cost. Prolonged antiplatelet therapy may be unnecessary with

nab-paclitaxel owing to short-term exposure and evidence of complete neointimal healing in animals.¹⁷ Furthermore, this approach would be applicable with any currently available stent.

Conclusions

This study explored the first clinical use of intravenous *nab*-paclitaxel for the reduction of in-stent restenosis in patients with *de novo* coronary artery lesions. *nab*-Paclitaxel doses <70 mg/m² appeared to be safe and feasible for further investigation; the side effects associated with higher doses were mild to moderate in nature. Larger studies exploring intravenous and intracoronary *nab*-paclitaxel are under way.

Acknowledgments

We thank Paul Bhar, MS, and Alicia Clawson, MS, for statistical analyses and Susan A. Thomas, ELS, for writing assistance.

References

1. Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, et al.: TAXUS I: Six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for *de novo* coronary lesions. *Circulation* 2003;107:38–42
2. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, et al.: Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions (TAXUS II). *Circulation* 2003;108:788–794
3. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, et al.: One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: The TAXUS IV trial. *Circulation* 2004;109:1942–1947
4. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, et al.: A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease (TAXUS IV). *N Engl J Med* 2004;350:221–231
5. Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, et al.: Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* 2005;23:7794–7803
6. Desai N, Trieu V, Yao R, Labao E, Soon-Shiong P: Increased endothelial transcytosis of nanoparticle albumin-bound paclitaxel (ABI-007) by gp60-receptors: A pathway inhibited by taxol. *27th Annual San Antonio Breast Cancer Symposium*, San Antonio, Texas, December 8–11, 2004 (abstr 1071)
7. Damascelli B, Cantu G, Mattavelli F, Tamplenizza P, Bidoli P, et al.: Intraarterial chemotherapy with polyoxyethylated castor oil free paclitaxel, incorporated in albumin nanoparticles (ABI-007): Phase II study of patients with squamous cell carcinoma of the head and neck and anal canal: Preliminary evidence of clinical activity. *Cancer* 2001;92(10):2592–2602
8. Nyman DW, Campbell KJ, Hersh E, Long K, Richardson K, et al.: Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. *J Clin Oncol* 2005;23:7785–7793
9. Blum JL, Savin MA, Edelman G, Phippen JE, Robert N, et al.: Long term disease control in taxane-refractory metastatic breast cancer treated with *nab* paclitaxel. *Proc Am Soc Clin Oncol* 2004;23:12 (abstr 543)
10. O'Shaughnessy JA, Blum JL, Sandbach JF, Savin M, Fenske E, et al.: Weekly nanoparticle albumin paclitaxel (Abraxane) results in long-term disease control in patients with taxane-refractory metastatic breast cancer. Presented at the *27th Annual San Antonio Breast Cancer Symposium*, San Antonio, Texas, December 8–11, 2004
11. Ibrahim NK, Samuels B, Page R, Doval D, Patel KM, et al.: Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer. *J Clin Oncol* 2005;23:6019–6026
12. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, March 31, 2003 (<http://ctep.cancer.gov>), Publish Date: December 12, 2003
13. Rodriguez AE, Alemparte MR, Vigo CF, Pereira CF, Llauroadé C, et al.: Pilot study of oral rapamycin to prevent restenosis in patients undergoing coronary stent therapy: Argentina Single-Center Study (ORAR Trial). *J Invasive Cardiol* 2003;15:581–584
14. Hausleiter J, Kastrati A, Mehilli J, Vogeser M, Zohlnhöfer D, et al. (OSIRIS investigators): Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis. The Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) Trial. *Circulation* 2004;110:790–795
15. Waksman R, Ajani AE, Pichard AD, Torguson R, Pinnow E, et al. (ORBIT investigators): Oral rapamycin to inhibit restenosis after stenting of *de novo* coronary lesions: The Oral Rapamune to Inhibit Restenosis (ORBIT) Study. *J Am Coll Cardiol* 2004;44:1386–1392
16. Chaves AJ, Sousa AGMR, Mattos LA, Abizaid A, Feres F, et al.: Pilot study with an intensified oral sirolimus regimen for the prevention of in-stent restenosis in *de novo* lesions: A serial intravascular ultrasound study. *Catheter Cardiovasc Interv* 2005;66:535–540
17. Kolodgie FD, John M, Khurana C, Farb A, Wilson PS, et al.: Sustained reduction of in-stent neointimal growth with the use of a novel systemic nanoparticle paclitaxel. *Circulation* 2002;106:1195–1198