Journal of the American College of Cardiology
© 2004 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 44, No. 7, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.06.069

Clinical Trials

Oral Rapamycin to Inhibit Restenosis After Stenting of De Novo Coronary Lesions

The Oral Rapamune to Inhibit Restenosis (ORBIT) Study

Ron Waksman, MD,* Andrew E. Ajani, MD,† Augusto D. Pichard, MD,* Rebecca Torguson, BS,* Ellen Pinnow, MS,* Daniel Canos, MPH,* Lowell F. Satler, MD,* Kenneth M. Kent, MD, PHD,* Pramod Kuchulakanti, MD,* Chrysoula Pappas, MD,* Louise Gambone, RN,* Neil Weissman, MD,* Maureen C. Abbott, MS,* Joseph Lindsay, MD*

Washington, DC; and Melbourne, Australia

OBJECTIVES The aim of this study was to establish safety and feasibility of oral Rapamycin at two doses—2 mg and 5 mg—in achieving low rates of repeat target lesion revascularization (TLR) in de novo native coronary artery lesions.

BACKGROUND Drug-eluting stents have shown the ability to limit restenosis. Oral Rapamycin is an alternative strategy that can target multiple coronary lesions suitable for treatment with any approved metal stent and at potentially lower cost.

METHODS The Oral Rapamune to Inhibit Restenosis (ORBIT) study is an open-label study of 60 patients with de novo lesions treated with bare metal stents in up to two vessels. After a loading dose of 5 mg, patients received a daily dose of 2 mg (n = 30) and 5 mg (n = 30) for 30 days. Six-month angiographic, intravascular ultrasound (IVUS), and clinical follow-up were conducted.

RESULTS Baseline clinical and procedural characteristics were similar: 10% of patients in the 2-mg group and 30% in the 5-mg group did not complete the course; 43% in the 2-mg group and 66% in the 5-mg group had side effects. At six-month follow-up, late loss (0.6 ± 0.5 mm vs. 0.7 ± 0.5 mm; p = NS), in-stent binary restenosis (7.1% vs. 6.9%; p = NS), in-stent percent volume obstruction by IVUS (29% vs. 24%; p = NS), and clinically driven TLR (14.3% vs. 6.9%; p = NS) were similar in 2-mg and 5-mg groups.

CONCLUSIONS Oral Rapamycin for the prevention of restenosis is safe, feasible, and associated with low rates of repeat revascularization. Although associated with certain side effects, it may be considered for patients undergoing multivessel stents if proven in larger randomized studies. (J Am Coll Cardiol 2004;44:1386–92) © 2004 by the American College of Cardiology Foundation

While coronary stenting has become standard of care for percutaneous interventions (PCIs), in-stent restenosis has persisted as a major obstacle. The prevention of restenosis has focused on inhibition of smooth muscle cell (SMC) division. The development of drug-eluting stents has allowed stents to be used as vehicles for prolonged and sufficient intramural drug delivery. Clinical efficacy and safety have been established for simple lesion morphologies using the Rapamycin-eluting stent (Cypher, Cordis, Miami, Florida), which incorporates a Rapamycin polymer onto bare metal (1–7). However, as the drug-eluting stent technology is limited to a stent platform, it may cause vessel toxicity with the potential development of aneurysms, edge effect, thrombosis, and stent malapposition (8–10). Although clinical results are encouraging, this technology, when applied to multivessel disease, is expensive and not economically sustainable. Rapamycin (sirolimus) is a natural macrocyclic lactone with potent immunosuppressive and anti-proliferative activity that was approved by the Food and Drug Administration in 1999 for prophylaxis against renal transplant rejection (11–17).

A number of preclinical studies support the use of systemic administration of Rapamycin in reducing SMC growth, the mediator of neointimal proliferation (18–22). Preclinical studies have demonstrated reduction of neointima formation after balloon injury in the porcine and the rabbit models of restenosis with the use of Rapamycin (18) and its analogue everolimus (Novartis Pharmaceuticals Corp., East Hanover, New Jersey) (19).

Oral Rapamycin is an alternative delivery strategy that can target multiple coronary lesions that are targets for catheter-based revascularization with any approved metal stent and with potentially lower cost. The aim of this pilot study was to establish the safety and feasibility of oral Rapamycin at two dosing strategies (2 and 5 mg) in achieving low rates of repeat target lesion revascularization (TLR) in de novo native coronary artery lesions.

From the *Cardiovascular Research Institute, Washington Hospital Center, Washington, DC; and the †Royal Melbourne Hospital and NHMRC Centre of Clinical Research Excellence in Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia.

Manuscript received April 6, 2004; revised manuscript received May 25, 2004, accepted June 22, 2004.

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
IVUS = intravascular ultrasound
MI = myocardial infarction
MLD = minimal luminal diameter
ORAR = Oral Rapamycin to Prevent Restenosis in Patients Undergoing Coronary Stent Therapy trial
ORBIT = Oral Rapamune to Inhibit Restenosis study
OSIRIS = Oral Sirolimus to Inhibit Recurrent In-stent Stenosis trial
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
SMC = smooth muscle cell
TLR = target lesion revascularization
TVR = target vessel revascularization

METHODS

This clinical trial was sponsored by the Medlantic Research Institute at Washington Hospital Center, Washington, DC. The study was approved by the institutional review board and monitored by an independent reviewer. A written informed consent was obtained from all patients before the study drug was administered. A clinical events committee independently adjudicated all clinical events in a blinded fashion.

Patient population. Oral Rapamune to Inhibit Restenosis (ORBIT) is an open-label study of 60 patients with de novo coronary artery stenosis treated with stent implantation in up to two vessels. Patients were enrolled between October 2001 and November 2002. The first 30 patients (49 lesions) received rapamycin 2 mg/day for 30 days, and the second 30 patients (37 lesions) received rapamycin 5 mg/day for 30 days. The loading dose for both regimens was 5 mg given either immediately before or after the intervention. Angiographic and clinical follow-up were performed at six months.

Inclusion criteria were age >18 years, stable or unstable angina with evidence of ischemia, treatment of de novo lesions in ≤2 coronary arteries, target lesion 2.5 to 4.0 mm in diameter, target lesion 15 to 30 mm in length (visual estimate), left ventricular ejection fraction ≥20%, and condition of patient as being an acceptable candidate for coronary artery bypass graft surgery (CABG).

Exclusion criteria were unprotected left main stenosis, ostial target lesion, in-stent restenotic lesion or prior stent within 5 mm of target lesion, angiographic evidence of thrombus, totally occluded vessel (Thrombolysis In Myocardial Infarction level 0), impaired renal function (creatinine >2.5 mg/dl), hemodynamic instability (hypotension), bifurcation lesions, excess co-morbid illness, contraindications (i.e., allergy) for drug treatments, active peptic ulcer or upper gastrointestinal bleeding, and status of patient as currently being treated with immunosuppressant therapy.

Study definitions. Q-wave myocardial infarction (MI) was defined by the presence of new pathologic Q waves on the electrocardiogram associated with an elevation of total creatinine kinase elevation at least 2 times the upper normal values. Non–Q-wave MI was defined as a total creatinine kinase elevation ≥2 times normal, with an elevation of MB isoenzyme of at least 3 times the upper normal value without new Q waves. Angiographic binary restenosis at follow-up was defined as ≥50% diameter narrowing within the stent and in the segment including the stent plus its edges (within 5 mm). Measurements were performed of the reference vessel, the stented segment, and the lesion segment including the edges of the stent. A lumen diameter of 0 mm was imputed in the presence of a total occlusion at baseline or at follow-up. Acute gain (in mm) was defined as the change in the stent minimum luminal diameter (MLD) from baseline to the final procedural angiogram. Late loss (in mm) was defined as the change in stent MLD from the final to the follow-up angiogram, and the arithmetic loss index within the stent was defined as late loss/acute gain. Leucopenia was defined as white cell count below 3×10^9/l.

Study end points. The primary end point of this study was angiographic restenosis at six months after procedure. Secondary end points included TLR, target vessel revascularization (TVR), and composite major adverse cardiac events (death, MI [Q-wave and non–Q-wave], CABG, or repeat TLR) at six months after procedure and intravascular ultrasound (IVUS) end points including percent of stent volume obstruction (neointima). A drug safety profile was conducted, and adverse reactions were adjudicated and recorded.

Quantitative coronary angiography (QCA) was performed to assess in-stent and in-lesion MLD and late lumen loss at six months after the procedure using the CMS-GFT system (Medis, Leiden, the Netherlands). The QCA was performed before the procedure, after the procedure, and for the six-month follow-up angiogram.

Intravascular ultrasound studies were performed after intracoronary administration of 200 μg of nitroglycerin with commercially available IVUS system (Boston Scientific Corp./Scimed, Natick, Massachusetts). The IVUS catheter was advanced distal to the lesion, and imaging was performed retrograde, back to the proximal reference at an automatic transducer pullback speed of 0.5 mm/s. Quantitative volumetric IVUS analysis was performed in an independent core laboratory. With the use of computerized planimetry software (TapeMeasure, INDEC Systems Inc., Capitola, California), stent and reference segments were measured every 1 mm. Reference segment external elastic membrane (EEM), lumen, and plaque and media (EEM-lumen) areas were measured over a 10-mm length adjacent to stent edge. Stent, lumen, and intimal hyperplasia (stent-lumen) areas were measured every 1 mm within the stented segment, and volumes were calculated using Simpson's rule. Intimal hyperplasia volumes were corrected for stent length by dividing intimal hyperplasia by stent length.

Statistical analysis. Continuous variables were expressed as mean ± SD, and categorical data were expressed as percentages. Continuous variables were compared using

Table 1. Baseline Clinical, Lesion, and Procedural Characteristics

	Rapamycin 2 mg n = 30 Patients	Rapamycin 5 mg n = 30 Patients	p Value
Age, yrs (mean ± SD)	59.7 ± 10.3	59.7 ± 9.7	1.0
Number of males, n (%)	26 (87)	25 (83)	0.72
Smoking history, n (%)	6 (20)	6 (20)	1.0
History of cerebrovascular disease, n (%)	3 (10)	0 (0)	0.24
History of diabetes, n (%)	4 (13)	7 (23)	0.31
Oral hypoglycemic therapy, n (%)	3 (10)	4 (13)	0.69
Insulin-requiring, n (%)	0 (0)	2 (7)	0.49
Hypertension, n (%)	19 (63)	21 (70)	0.58
Hyperlipidemia, n (%)	28 (93)	27 (93)	0.97
Prior cardiac bypass graft surgery, n (%)	2 (7)	1 (3)	1.0
Prior myocardial infarction, n (%)	6 (20)	4 (13)	0.49
Prior PCI, n (%)	7 (24)	7 (23)	0.94
Unstable angina, n (%)	19 (63)	12 (40)	0.07
CCS* III or IV, n (%)	16 (53)	11 (37)	0.19
Left ventricular ejection fraction	0.54 ± 0.10	0.51 ± 0.06	0.21
Number of diseased vessels	n = 29*	n = 30	
Single, n (%)	8 (28)	20 (66)	0.003
Two, n (%)	16 (55)	8 (27)	0.03
Three, n (%)	5 (17)	2 (7)	0.21
Number of diseased vessels	1.90 ± 0.67	1.40 ± 0.62	0.005
Lesion Characteristics	**n = 49 Lesions**	**n = 37 Lesions**	
Left anterior descending, n (%)	21 (43)	16 (43)	0.97
Circumflex, n (%)	14 (29)	5 (14)	0.10
Right coronary artery, n (%)	14 (29)	16 (43)	0.16
Lesion length, mm	14.12 ± 6.75	13.57 ± 4.84	0.67
Reference vessel diameter, mm	3.00 ± 0.44	3.09 ± 0.51	0.36
Procedural strategy, n (%)			
Stents per patient	1.6 ± 0.5	1.3 ± 0.5	0.02
Atherectomy, n (%)	8 (16)	2 (5)	0.18
Direct stenting, n (%)	20 (41)	21 (57)	0.14
Pre-balloon, n (%)	9 (18)	3 (8)	0.17
Cutting balloon, n (%)	12 (25)	5 (14)	0.21

*Data for one patient was not entered on this question.
CCS = Canadian Cardiovascular Society angina class; PCI = percutaneous coronary intervention.

Student *t* test, and categorical variables were compared using chi-square statistics or Fisher exact test. Analyses on variables containing non-independent observations were analyzed using the SAS GENMOD procedure. All analyses were performed by intent to treat. A p value of 0.05 was considered statistically significant.

RESULTS

Characteristics of study population. The two cohorts of 2 and 5 mg Rapamycin were matched for baseline clinical and procedural characteristics (Table 1). Patients treated with 5 mg Rapamycin compared with the 2 mg cohort had a lower number of diseased vessels (1.4 ± 0.6 mm vs. 1.9 ± 0.7; $p < 0.01$) and had less lesions treated overall. The coronary lesions were evenly distributed in the native coronary system. Lesion length (14.1 ± 6.8 mm vs. 13.6 ± 4.8 mm; p = NS) and reference vessel diameter (3.0 ± 0.4 mm vs. 3.1 ± 0.5 mm; p = NS) were similar in the 2- and 5-mg groups. The predominant interventional approach to treatment was direct stenting in both cohorts (48% overall).

In-hospital outcomes. No in-hospital deaths or Q-wave MIs occurred in either cohort. Three patients in the 2-mg (10.0%) and two patients in the 5-mg (6.7%) Rapamycin groups sustained non–Q-wave MIs. There were no reported abrupt closures, and no patients needed emergent CABG or repeat in-hospital PCI.

Angiographic and IVUS results. Six-month angiographic analysis was performed in 86% of lesions (42 of 49) in the 2-mg Rapamycin cohort and 78% of lesions (29 of 37) in the 5-mg Rapamycin cohort (Table 2). The MLD at follow-up (2.3 ± 0.6 mm vs. 2.3 ± 0.8 mm; p = NS) and late loss (0.6 ± 0.6 mm vs. 0.7 ± 0.5 mm; p = NS) were not significantly different in the two groups—indicating no dose-response effect.

Intravascular ultrasound analysis was performed in 68% of lesions (32 of 47) in the 2-mg Rapamycin cohort and 43% of lesions (16 of 37) in the 5-mg Rapamycin cohort. No dose response effect was seen within the 2- and 5-mg cohorts with similar six-month intimal hyperplasia volume corrected for stent length (2.35 ± 1.31 mm^3 vs. 2.16 ± 1.42 mm^3; p = NS) and percent volume obstruction (29% vs. 24%; p = NS). There was no evidence of stent malapposition, and most struts were covered by a neointima as demonstrated by the neointimal volume in this cohort.

Table 2. Angiographic Characteristics—Pre-Procedural, Post-Intervention, and at Six Months

Parameters	Rapamycin 2 mg n = 49 Lesions (Pre and Post) n = 42 Lesions (F/U)	Rapamycin 5 mg n = 37 Lesions (Pre and Post) n = 29 Lesions (F/U)	p Value
Minimal luminal diameter, mm			
Pre	1.08 ± 0.61	1.36 ± 0.52	0.033
Post	2.88 ± 0.57	2.95 ± 0.52	0.683
Six-month F/U	2.29 ± 0.61	2.27 ± 0.75	0.781
Diameter stenosis, %			
Pre	62.07 ± 18.03	55.5 ± 15.34	0.063
Post	13.12 ± 6.76	9.54 ± 5.38	0.010
Six-month F/U	21.53 ± 15.64	22.72 ± 23.72	0.935
Binary restenosis			
In-stent	3/42 (7.1%)	2/29 (6.9%)	0.524
In-lesion	2/42 (4.8%)	2/29 (6.9%)	0.897
Late loss, mm			
In-stent	0.60 ± 0.54	0.71 ± 0.49	0.582
In-lesion	0.60 ± 0.61	0.68 ± 0.56	0.783

F/U = follow-up.

Further, not all patients were available for angiographic or IVUS follow-up; however, those who were unavailable were asymptomatic.

Subset analysis of patients (n = 38) who had IVUS follow-up with multi- versus single-stent showed similar corrected intimal hyperplasia volumes between these two groups, respectively (2.27 ± 0.93 vs. 2.08 ± 1.3; p = 0.7). Similar subset analysis of late loss in patients with QCA (n = 53) did not show any statistically significant difference between multi- versus single-stent cohorts (0.7 ± 0.4 vs. 0.5 ± 0.5; p = 0.18). Within an individual patient with multiple stents (n = 13), IVUS analysis showed a similar amount of corrected intimal hyperplasia in each lesion (mean 2.26 vs. 2.07 mm^3; p = 0.60). The mean difference of corrected intimal hyperplasia volume between each lesion within an individual patient was −0.191 mm^3.

Six-month clinical outcomes. Clinical follow-up at six months was available in 29 patients (96%) in the 2-mg Rapamycin group and 30 patients (100%) in the 5-mg Rapamycin cohort (Table 3). One patient did withdraw from the 2-mg cohort and was, therefore, unavailable for six-month follow-up. There were no documented deaths, Q-wave or non–Q-wave MIs beyond hospital discharge. The rate of clinically driven TLR (defined as revascularization at the target site associated with any of the following: positive functional ischemia study, ischemic symptoms, and an angiographic minimum lumen diameter stenosis >50% by QCA or revascularization of a target site with diameter stenosis >70% by QCA without either angina or a positive functional study was 14.3% vs. 6.9%; p = 0.33) and TVR (including CABG to non-restenotic vessels (16.7% vs. 20.6%; p = 0.67) were similar in the two groups. The high rate of TVR in this study was a result of patients who went to CABG and had complete revascularization including vessels treated in the study that were non-restenotic at the time of the surgery. Overall, seven patients (three in 2-mg and four in 5-mg group) had CABG to nine target vessels at six months. Although angiographic stenosis did not meet the definition of binary restenosis, one patient in the 2-mg group and three in the 5-mg group had bypass grafts to ORBIT vessels at the time of CABG at the discretion of the surgeons. These patients were referred to elective CABG

Table 3. Major Clinical Events at Six Months

	Rapamycin 2 mg n = 29 Patients	Rapamycin 5 mg n = 30 Patients	p Value
Cardiac death, n (%)	0/29 (0%)	0/30 (0%)	—
Non-cardiac death, n (%)	0/29 (0%)	0/30 (0%)	—
Q-wave MI, n (%)	0/29 (0%)	0/30 (0%)	—
Non–Q-wave MI, n (%)	3/29 (10.0%)	2/30 (6.7%)	0.61
MACE	7/29 (24%)	6/30 (20.0%)	0.71
Repeat revascularization	n = 42 lesions	n = 29 lesions	
TVR, n (%)	7/42 (16.7%)	6/29 (20.6%)	0.67
TVR-CABG	4/42 (9.5%)	5/29 (17.2%)	0.34
TVR-PCI	3/42 (7.1%)	1/29 (3.4%)	0.51
TLR, n (%)	6/42 (14.3%)	2/29 (6.9%)	0.33
TLR-CABG	3/42 (7.1%)	2/29 (6.9%)	0.97
TLR-PCI	3/42 (7.1%)	0/29 (0%)	0.14

CABG = coronary bypass graft surgery; MACE = major adverse cardiac events; MI = myocardial infarction; PCI = percutaneous coronary intervention; TLR = target lesion revascularization; TVR = target vessel revascularization.

Table 4. Laboratory Index at Baseline and 30 Days

	In-Hospital		30 Days	
	Rapamycin 2 mg	Rapamycin 5 mg	Rapamycin 2 mg	Rapamycin 5 mg
Rapamycin level, ng/ml	5.2 ± 3.1*	6.4 ± 6.4*	6.4 ± 4.2	18.7 ± 12.7†
Total cholesterol, mg/dl	196 ± 38	178 ± 36	170 ± 34	201 ± 40
HDL, mg/dl	42 ± 9	42 ± 15	46 ± 9	42 ± 5
LDL, mg/dl	124 ± 35	107 ± 43	91 ± 32	118 ± 38†
Triglyceride, mg/dl	158 ± 92	163 ± 72	185 ± 131	236 ± 105

*Serum level at day 1; †$p < 0.05$ vs. 2 mg Rapamycin at 30 days.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

due to progression of disease in other vessels including one left main disease. Three patients in the 2-mg and one patient in the 5-mg group had repeat PCI at six months. In the 2-mg group, all three PCIs were TLRs, and in the 5-mg group it was TVR-PCI. The pattern of in-stent restenosis was focal, diffuse, and total occlusion in each of the three patients in the 2-mg group. These restenotic lesions were treated with cutting balloon, repeat stenting to optimize the result, and brachytherapy in one patient. The patient in the 5-mg group had no restenosis of the initial stent implanted to right posterior descending artery, but a proximal lesion progressed that required PCI.

Drug tolerance and side-effect profile. Tolerance of 2 mg was better than 5 mg with 27 of 30 patients (90%) completing four weeks of Rapamycin (26.7 ± 7.8 days) in the 2-mg group; however, one-third of the patients (10 of 30, 33%) in the 5-mg group did not complete the course (22 ± 11.7 days) ($p = 0.06$). Serum rapamycin levels at days 1 and 30 are shown in Table 4. Side effects were reported in 13 of 30 patients (43.3%) in the 2-mg group and 20 of 30 (66.7%) in the 5-mg group. More than one symptom was reported in six patients in the 5-mg group (four patients had two symptoms each, and two patients had three symptoms each) and none in the 2-mg group. The symptoms were classified as: mild—probably drug-related, tolerated, and controlled with palliative therapy; moderate—definitely related to the drug, but not requiring discontinuation, higher in intensity but controlled with palliative therapy; and severe—definitely related to the drug and requiring discontinuation of the drug. The rates of mild and moderate symptoms were 61.5%, 30.7% in 2-mg group and 75%, 14.3% in 5-mg group, respectively. Severe symptoms were reported in 7.6% and 10.7% in 2- and 5-mg groups, respectively, which required withdrawal of the study drug. In addition to the patients with severe symptoms, two other patients in the 2-mg group and seven other patients in the 5-mg group discontinued the drug before completing the course. Table 5 shows the details of side effects reported. No significant leucopenia was detected in either cohort at 30-day follow-up. Side effects resulting in Rapamycin discontinuation included rash, mouth ulcers, diarrhea, and fatigue. All side effects remitted with cessation of medication. Hypertriglyceridemia was evident, particularly in the 5-mg Rapamycin group, without clinical consequences (Table 4). The increase in the triglycerides represents 17 patients who had more than a 20-U increase in their triglycerides. Of these patients, 15 had lipid studies done after 30 days. All but one patient (baseline triglyceride level of 93; 30-day triglyceride level of 158; 6-month triglyceride level of 155) returned to their pre-procedure triglyceride

Table 5. Report of Side Effects and Their Severity Associated With the Study Medication

Side Effect	2-mg Group (n = 30)			5-mg Group (n = 30)		
None, n (%)	17 (56.6)			10 (33.3)		
Reported, n (%)	13 (43.3)			20 (66.7)†		
	Severity					
Individual Symptoms*	Mild	Moderate	Severe	Mild	Moderate	Severe
Nausea	1	0	0	0	0	0
Vomiting	0	1	0	1	0	0
Diarrhea	3	1	0	5	0	1
Blood diarrhea	0	0	1	0	0	0
Gum sores	3	1	0	3	2	1
Rashes	1	1	0	9	1	0
Fatigue	0	0	0	0	1	0
Elevated triglycerides	0	0	0	0	0	1
Leucopenia	0	0	0	2	0	0
Hepatic dysfunction	0	0	0	1	0	0
Total, n (%)‡	8 (61.5)	4 (30.7)	1 (7.6)	21 (75.0)	4 (14.3)	3 (10.7)

*Each side effect is counted separately in every patient; †Four patients had two symptoms each, and two patients had three symptoms each; ‡Percentages expressed in relation to total number of symptoms in each group.

levels. Six-month follow-up suggested that there were no clinical consequences to the patients who presented with hypertriglyceridemia. Body mass index did not have any significant effect on restenosis, drug level at 30 days, or the number of patients experiencing side effects related to the drug. Further, the blood levels of Rapamycin were not correlated to the rate of side effects (chi-square test for trend: $p = 0.48$).

DISCUSSION

The principal findings of this study include: 1) oral Rapamycin administration is feasible for 30 days for restenosis prevention of de novo coronary lesions; 2) the current dosing strategies of 2 and 5 mg Rapamycin resulted in low and similar rates of six-month TLR and TVR; 3) no dose response was seen in the two Rapamycin cohorts as evidenced by similar rates of late loss and IVUS percent volume obstruction at six months; 4) hypertriglyceridemia was seen predominantly in the 5-mg Rapamycin group without clinical consequences; and 5) severe side effects attributable to rapamycin were infrequent.

Single-digit restenosis rates have been achieved with Rapamycin-eluting stents (1–7). While the evidence for effectiveness of drug-eluting stents is mounting, their long-term durability and use for multivessel disease remain unknown. Although locally delivered Rapamycin is the subject of intensive investigation, only one published study has assessed oral Rapamycin therapy and found no clinical benefit when administered to patients at high risk for restenosis (23). This cohort of 15 patients had recalcitrant in-stent restenosis that had either failed or were not candidates for intracoronary radiation, a population markedly different from patients with de novo coronary lesions. Lack of efficacy seen with oral Rapamycin in that study may have been due to inadequate drug dosing (2 mg/day for 30 days). Further, serum Rapamycin levels were not reported, and there are no data to support the efficacy of Rapamycin-eluting stents for this subset of patients. It is possible that patients with refractory restenosis, such as those who failed radiation therapy, will not respond well to either eluting or oral Rapamycin. In contrast, the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) (24) and Oral Rapamycin to Prevent Restenosis in Patients Undergoing Coronary Stent Therapy (ORAR) (25) trials showed beneficial effects in restenotic and de novo lesions, respectively.

The late loss reported in RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL), SIRIUS, and TAXUS IV ranged from -0.01 ± 0.33 mm to 0.39 ± 0.5 mm with drug-eluting stents and 0.80 ± 0.53 mm to 1.0 ± 0.7 mm with bare metal stents (6,7). The late loss with oral Rapamycin (0.64 ± 0.52 mm) in the present study was higher than that of drug-eluting stents but was still lower than reported historic controls of standard stent cohorts from these studies. This reduction in the late loss translated into low in-stent (7.1% vs. 6.9%; p = NS) and in-lesion (4.8% vs. 6.9%; p = NS) binary restenosis rates for both 2-mg and 5-mg groups. There were no early or late stent thromboses and no late aneurysms as expected.

In-stent restenosis and cardiac transplantation vasculopathy are both characterized by intense intimal proliferation secondary to SMC proliferation. Rapamycin targets central regulators of cell cycle progression in vascular SMCs, including the cyclin-dependent kinase inhibitor $p27^{kip1}$ (21,22). Rapamycin combines anti-proliferative and anti-migratory properties with immunosuppressant activity and has been shown to prevent and treat graft (cardiac transplant) vasculopathy (26). In an open-labeled study of 46 patients with graft vasculopathy, oral Rapamycin reduced the number of primary end points (composite of death, MI, need for revascularization, or angiographic deterioration) and secondary end points (cardiac hospitalizations), with no increase in rate of infection. This effect of rapamycin was seemingly independent of its immunosuppression, implying a predominant anti-proliferative action (27). Our study supports the feasibility of systemic Rapamycin therapy in the prevention of neointimal proliferation.

To our knowledge, our study is among the first to report of Rapamycin for restenosis prevention of de novo coronary lesions. This study has the inherent limitations of a single-center registry without a control group and a limited follow-up to six months. The lack of statistically significant findings in the study could be due to the small sample size. Further, not all patients were available for angiographic and IVUS follow-up; however, those who were unavailable were asymptomatic.

Interestingly, for patients who completed four weeks of Rapamycin treatment, dose levels did not have any effect on restenosis outcome variables (chi-square test for trend: 2 mg, p = 0.57; 5 mg, p = 0.64). Further, the duration of Rapamycin for patients who withdrew from the drug before the 30 days also did not affect restenosis (chi-square test for trend: 2 mg, p = 0.43; 5 mg, p = 0.76). The cumulative dose of Rapamycin did not have any significant effect on restenosis (chi-square test for trend: p = 0.36).

Thus, the study posed several questions relating to optimal and therapeutic loading doses as well as time and duration of drug administration. The current dose used in patients after renal transplantation is 2 mg/day, and it is possible that a dose of 5 mg is not necessary for the vascular application, because no clinical and angiographic differences were detected between the 2- and 5-mg groups in the present study. Because dose levels and duration of treatment did not have an effect on restenosis outcome variables, perhaps it is the loading dose that can make the difference. The OSIRIS study supports pretreatment, higher loading doses, and short treatment times for patients with in-stent restenosis. Implementation of this strategy may improve the outcome of de novo lesions as well. It is also unclear whether blood levels of the drug should be monitored. For renal

transplant patients, a Rapamune level >8 ηg/ml is recommended. The ORAR study did show beneficial effects when blood levels were >8 ηg/ml. In the present study, we could not detect correlation between the Rapamune level and clinical events or late loss. Nevertheless, it is possible that larger sample sizes would have detected optimal blood levels. If so, this is a deficiency of this strategy, which would involve extra costs and inconvenience.

Finally, the cost of 2 mg of oral rapamycin for 30 days is nearly $500 per patient. This is significantly lower than the current cost of drug-eluting stents. This difference is more pronounced when multiple stents are required to treat multivessel disease. Another potential benefit of the drug is its anti-inflammatory properties, which may prove beneficial in the setting of acute coronary syndrome in the vulnerable patients.

Conclusions. In this preliminary analysis, oral Rapamycin administration for the prevention of restenosis is safe and feasible. Lower rates of restenosis and later loss than anticipated were observed in both dosing strategies (without dose-response). The ORBIT II study, an international, multicenter, randomized trial, has been initiated and will determine whether systemic oral administration of Rapamycin will be a therapeutic option for patients undergoing PCI.

Reprint requests and correspondence: Dr. Ron Waksman, 110 Irving Street, NW, Suite 4B-1, Washington, DC 20010. E-mail: ron.waksman@medstar.net.

REFERENCES

1. Lemos PA, Lee C, Degertekin M, et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. J Am Coll Cardiol 2003;41:2093–9.
2. Sousa JE, Costa MA, Sousa AG, et al. Two-year angiographic and intravascular ultrasound follow-up after implantation of sirolimus-eluting stents in human coronary arteries. Circulation 2003;107:381–3.
3. Degertekin M, Regar E, Tanabe K, et al. Sirolimus-eluting stent for treatment of complex in-stent restenosis: the first clinical experience. J Am Coll Cardiol 2003;41:184–9.
4. Regar E, Serruys PW, Bode C, et al., for the RAVEL Study Group. Angiographic findings of the multicenter Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. Circulation 2002;106:1949–56.
5. Degertekin M, Serruys PW, Foley DP, et al. Persistent inhibition of neointimal hyperplasia after sirolimus-eluting stent implantation: long-term (up to 2 years) clinical, angiographic, and intravascular ultrasound follow-up. Circulation 2002;106:1610–3.
6. Serruys PW, Degertekin M, Tanabe K, et al., for the RAVEL Study Group. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. Circulation 2002; 106:798–803.
7. Morice MC, Serruys PW, Sousa JE, et al., for the RAVEL Study Group. Randomized study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions: a randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
8. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
9. Virmani R, Liistro F, Stankovic G, et al. Mechanism of late in-stent restenosis after implantation of a paclitaxel derivate-eluting polymer stent system in humans. Circulation 2002;106:2649–51.
10. Liistro F, Stankovic G, Di Mario C, et al. First clinical experience with a paclitaxel derivate-eluting polymer stent system implantation for in-stent restenosis: immediate and long-term clinical and angiographic outcome. Circulation 2002;105:1883–6.
11. Groth CG, Backman L, Morales JM, et al. Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine: Sirolimus European Renal Transplant study group. Transplantation 1999;67:1036–42.
12. Collier DS, Calne R, Thiru S, et al. Rapamycin in experimental renal allografts in dogs and pigs. Transplant Proc 1990;22:1674–5.
13. Granger DK, Cromwell JW, Chen SC, et al. Prolongation of renal allograft survival in a large animal model by oral rapamycin monotherapy. Transplantation 1995;59:183–6.
14. Almond PS, Moss A, Nakhleh R, et al. Rapamycin in a porcine renal transplant model. Ann NY Acad Sci 1993;685:121–2.
15. Morris RE, Meiser BM, Wu J, et al. Use of rapamycin for the suppression of alloimmune reactions in vivo: schedule dependence, tolerance induction, synergy with cyclosporine and FK 506, and effect on host-versus-graft and graft-versus-host reactions. Transplant Proc 1991;23:521–4.
16. Collier DS, Calne RY, Pollard SG, et al. Rapamycin in experimental renal allografts in primates. Transplant Proc 1991;23:2246–7.
17. Kahan BD, Murgia MG, Slaton J, et al. Potential applications of therapeutic drug monitoring of sirolimus immunosuppression in clinical renal transplantation. Ther Drug Monit 1995;17:672–5.
18. Gallo R, Padurean A, Jayaraman T, et al. Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. Circulation 1999;99:2164–70.
19. Farb A, John M, Acampado E, et al. Oral everolimus inhibits in-stent neointimal growth. Circulation 2002;106:2379–84.
20. Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. Circulation 2001;104: 2007–11.
21. Marx SO, Jayaraman T, Go LO, et al. Rapamycin-FKBP inhibits cell cycle regulators of proliferation in vascular smooth muscle cells. Circ Res 1995;76:412–7.
22. Poon M, Marx SO, Gallo R, et al. Rapamycin inhibits vascular smooth muscle cell migration. J Clin Invest 1996;98:2277–83.
23. Brara PS, Moussavian M, Grise MA, et al. Pilot trial of oral rapamycin for recalcitrant restenosis. Circulation 2003;107:1722–4.
24. Hausleiter J, Kastrati A, Mehilli J, et al. 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;110:790–5.
25. Rodríguez AE, Alemparte MR, Vigo CF, 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;15:581–4.
26. Poston RS, Billingham M, Hoyt EG, et al. Rapamycin reverses chronic graft vascular disease in a novel cardiac allograft model. Circulation 1999;100:67–74.
27. Mancini D, Pinney S, Burkhoff D, et al. Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation 2003; 108:48–53.