Brief Rapid Communications

Pilot Trial of Oral Rapamycin for Recalcitrant Restenosis

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Background—Sirolimus-coated stents are a promising new therapy for restenosis. We treated a select group of patients at especially high risk for restenosis with oral sirolimus.

Methods and Results—Patients were treated with an oral sirolimus-loading dose of 6 mg after coronary angioplasty, followed by 2 mg/d for 4 weeks. Serum electrolytes, lipid profile, renal panel, and complete blood cell count were measured at 1, 3, and 5 weeks after drug initiation. Oral sirolimus was prescribed to 22 patients who had a total of 28 lesions and were at high risk for restenosis. Of the 22 study patients, 11 (50%) discontinued oral sirolimus early because of side effects or laboratory abnormalities. Hypertriglyceridemia and leukopenia were the most frequent adverse events, occurring in 3 patients each. All adverse drug effects were reversible after discontinuation. Follow-up was obtained in 100% of patients at a mean of 9.9±1.8 months, ranging from 6.5 to 11.8 months. Target lesion revascularization (TLR) occurred in 15 of 28 lesions (53.6%) and 13 of 22 patients (59.1%). There was no difference in TLR for patients receiving a complete course of sirolimus (n=8; 72.7%) compared with patients who terminated treatment prematurely (n=5; 45.5%; P=NS). Clinically driven repeat cardiac catheterization was obtained in 15 (68.2%) patients; restenosis (>50% diameter stenosis at follow-up) was present in 13 (86.7%).

Conclusion—Oral sirolimus does not appear to provide benefit to patients with recalcitrant restenosis. Adverse drug effects are frequent, underscoring the importance of local drug delivery to achieve high tissue concentrations without systemic adverse drug effects. (Circulation. 2003;107:1722-1724.)

Key Words: restenosis ▪ angioplasty ▪ stents

In-stent restenosis is a significant limitation to stenting. Intracoronary radiation provides a meaningful reduction in clinical and angiographic stent restenosis; however, a significant number of patients have recalcitrant restenosis, despite radiation therapy.1–5 Recent data indicate that rapamycin-eluting stents are a promising treatment for restenosis.6,7 Rapamycin is a macrolyclic lactone that indirectly inhibits cell division and inhibits neointimal hyperplasia when delivered locally.8,9 Despite encouraging results using local, stent-based delivery of rapamycin, there are limitations to this approach, including patients who are not candidates for stents because of small vessel disease, vessel tortuosity, and allergy to thienopyridines.

The rapamycin-eluting stent as a local platform was inspired, in part, by animal models demonstrating the effectiveness of systemic rapamycin.10,11 We hypothesized that this drug, given orally, may be an effective alternative to local delivery for the prevention of restenosis. The objective of this study was to evaluate the safety and efficacy of oral rapamycin in patients with recalcitrant restenosis, most of whom had not responded to previous coronary radiation therapy.

Methods

Study Population
We studied 22 patients who received oral rapamycin to prevent a future episode of clinical restenosis. The study protocol was approved by the Human Subject Committee at Scripps Clinic. Entry criteria included patients with in-stent restenosis and who had not responded to intracoronary radiation or patients who were not candidates for intracoronary radiation.

Drug Regimen
Patients were placed on oral rapamycin with a loading dose of 6 mg, provided within 1 to 12 hours after percutaneous intervention. Patients were not pretreated to ensure confirmation of recurrent restenosis before initiation of drug therapy. Therapy was continued at a 2 mg/d dose for 30 days, with the intent to approximate the treatment duration of the slow-release rapamycin stent. This dose of rapamycin was chosen because it is the Food and Drug Administration-approved dose used in renal transplant patients. All patients also received aspirin (325 mg/d) and clopidogrel (75 mg/d) indefinitely.

Follow-Up Evaluation
Patients were discharged with a 30-day supply of oral rapamycin. Patients were instructed to have their blood drawn for complete blood cell count, metabolic panel, lipid panel, and liver function tests.
at weeks 1, 3, and 5. Telephone contact was obtained during these intervals to assess for any adverse side effects or laboratory abnormalities attributed to rapamycin. All subsequent angiography procedures were clinically driven and were at the discretion of the patient’s treating physician. Only angiograms obtained >4 months after the index procedure qualified for analysis unless restenosis was observed on an earlier angiogram.

**End Points**

The primary endpoint was clinical restenosis requiring target lesion revascularization (TLR). Secondary endpoints evaluated were death, myocardial infarction, and target vessel revascularization.

**Statistical Analysis**

Means and standard deviations were calculated for baseline characteristics and results of the study patients.

**Results**

From August 21, 2001, through February 1, 2002, 22 patients with a total of 28 target lesions were treated with oral rapamycin. Baseline characteristics are listed in Table 1. Patients had an average of 3.5±1.6 episodes of previous restenoses. Previous radiation failure occurred in 20 (90.9%) patients, and 2 (9.1%) patients were not candidates for radiation therapy (both because of very small and tortuous target vessels not considered accessible by radiation delivery catheters).

**Side Effects and Duration of Treatment**

Presumed medication side effects and reasons for discontinuation of rapamycin are described in Table 2. There were 11 (50%) patients who did not complete the full 30-day prescription. The average duration of oral rapamycin therapy before discontinuation of was 14.5±6.5 days. The most common reason for withdrawal of rapamycin was hypertriglyceridemia and leukopenia, each occurring in 3 (27.3%) patients. Early in the study, a patient was entered with a baseline triglyceride level of 1412 mg/dL (reference range <200 mg/dL). The patient was cautioned about the risks of hypertriglyceridemia but requested enrollment because of incessant restenosis. Oral rapamycin was discontinued after 8 days, and yet this patient’s triglycerides increased to 14 520 mg/dL. In the 2 other patients, triglycerides increased from 232 to 480 mg/dL and from 143 to 414 mg/dL. In the 3 patients with leukopenia, the absolute neutrophil count decrements were 1700 to 66 000 cells/µL, 7700 to 1666 cells/µL, and 4500 to 1277 cells/µL (reference range 1500 to 7800 cells/µL). The total white blood count decrements were 3.7 to 1.2 thousand/mm³, 9.1 to 3.4 thousand/mm³, and 5.7 to 3.1 thousand/mm³ (reference range 4.5 to 11.0 thousand/mm³). There were no clinical consequences of either hypertriglyceridemia or leukopenia. Other side effects resulting in rapamycin discontinuation were stomatitis, flu-like symptoms, and acne. All side effects remitted with cessation of medication.

**Follow-Up**

Follow-up was obtained in 100% of patients at a mean duration of 9.9±1.8 months (Table 3). The length of follow-up ranged from 6.5 to 11.8 months. There were no deaths or myocardial infarctions. TLR occurred in 15 of 28 lesions (53.6%) and 13 of 22 patients (59.1%). There was no difference in TLR between patients able to complete the prescribed 30-day course of oral rapamycin and patients who discontinued therapy early (Table 3). Target vessel revascularization was observed in 13 (59.1%) patients and non-target vessel revascularization occurred in 3 (13.6%) patients. Clinically driven angiography was obtained in 15 patients (68.2%) containing 20 target lesions (71.4%) at a mean of 5.1 months. Restenosis, defined as a diameter stenosis ≥50%, was observed in 13 patients (86.7%) and 15 lesions (75.0%) that underwent follow-up angiography.

**Discussion**

Recent multicenter, randomized trials report restenosis rates under 10% after implantation of both rapamycin- and taxol-eluting stents, and this local-based delivery system will likely
become a new standard of care.\textsuperscript{6,12,13} Given the profound efficacy of locally delivered rapamycin, we tested the effect of oral rapamycin in patients at high risk for restenosis. Our data suggests there is no clinical benefit when oral rapamycin therapy is administered to patients at high risk for restenosis. Subsequent TLR was required in 13 (59.1\%) of our study patients despite oral rapamycin therapy. Angiographic restenosis occurred in 86.7\% of patients undergoing follow-up angiograms. Because follow-up angiography was performed in only 68.2\% of patients, restenosis rates may have been underestimated. Even if efficacy of this systemic approach had been demonstrated, the frequent observation of adverse reactions would make oral rapamycin an unlikely therapeutic agent. The 30-day duration of therapy was only completed by 68.2\% of patients. Restenosis rates may have been insufficient, as it did not "mimic" the slow release sirolimus-eluting stent that results in approximately 80\% drug release at 28 days and 95\% at 90 days, with maintenance of arterial tissue concentration of about 1 ng/mg at 90 days. A surprisingly large number of patients discontinued oral sirolimus because of side effects. Clearly, the 1 patient with a baseline triglyceride level of 1412 mg/dL should not have been enrolled despite her numerous previous restenoses. It should be noted that many of the other side effects we observed were minor; therefore, substantially more patients may have completed a 30-day course of therapy if it was known to be effective. Because this was the first trial of oral rapamycin for this unproven indication, we had a very low threshold for discontinuing treatment when even minor side effects were observed. Nevertheless, efficacy was not improved in patients receiving the full 30-day course of therapy.

This is the first study to assess the effect of oral rapamycin therapy in patients undergoing percutaneous intervention. Because this study was early, we enrolled patients at exceptionally high risk for restenosis. Perhaps future studies targeting lower risk patients and/or a higher dose of rapamycin may be more successful. However, we believe our observation of frequent adverse effects and apparent lack of efficacy in this pilot trial make oral rapamycin an unlikely restenosis treatment. Our data underscore the advantages of a local stent-based delivery system, which provides a high local concentration of this potentially toxic medication while maintaining a low systemic dose.

\textbf{References}

Corrections

In the recent article, “Pilot Trial of Oral Rapamycin for Recalcitrant Restenosis” (Circulation. 2003;107:1722–1724), a sentence was incorrect. The sentence, “The study protocol was approved by the Human Subject Committee at Scripps Clinic,” should have stated: “Patients were initially treated with rapamycin as an off-label therapy. Human Subjects Committee approval was subsequently granted and written consent obtained from patients for a retrospective review of their medical records.” This study was not a prospective study, as may have been inferred from the article as written.

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In the recent In Memoriam for Arthur C. Guyton, MD (Circulation. 2003;107:2990–2992), the name of the author was incorrectly written as “John D. Hall, PhD.” The author of the In Memoriam is John E. Hall, PhD.

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In the recent article, “Short-Term Statin Therapy Improves Cardiac Function and Symptoms in Patients With Idiopathic Dilated Cardiomyopathy” (Circulation. 2003;108:839–843), the total number of patients was incorrect in the abstract. The sentence, “Sixty-three patients with symptomatic, nonischemic, dilated cardiomyopathy were randomly divided into 2 groups,” should have stated: “Fifty-one patients with symptomatic, nonischemic, dilated cardiomyopathy were randomly divided into 2 groups.”

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