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

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Background—Despite recent advances in interventional cardiology, including the introduction of drug-eluting stents for de novo coronary lesions, the treatment of in-stent restenosis (ISR) remains a challenging clinical issue. Given the efficacy of systemic sirolimus administration to prevent neointimal hyperplasia in animal models and to halt and even reverse the progression of allograft vasculopathy, the aim of the present double-blind, placebo-controlled study was to evaluate the efficacy of a 10-day oral sirolimus treatment with 2 different loading regimens for the prevention of recurrent restenosis in patients with ISR.

Methods and Results—Three hundred symptomatic patients with ISR were randomly assigned to 1 of 3 treatment arms: placebo or usual-dose or high-dose sirolimus. Patients received a cumulative loading dose of 0, 8, or 24 mg of sirolimus 2 days before and the day of repeat intervention followed by maintenance therapy of 2 mg/d for 7 days. Angiographic restenosis at 6-month angiography was the primary end point of the study. Restenosis was significantly reduced from 42.2% to 38.6% and to 22.1% in the placebo, usual-dose, and high-dose sirolimus groups, respectively (P=0.005). Similarly, the need for target vessel revascularization was reduced from 25.5% to 24.2% and to 15.2% in the placebo, usual-dose, and high-dose groups, respectively (P=0.08). The sirolimus blood concentration on the day of the procedure correlated significantly with the late lumen loss at follow-up (P<0.001).

Conclusions—In patients with ISR, an oral adjunctive sirolimus treatment with an intensified loading regimen before coronary intervention resulted in a significant improvement in the angiographic parameters of restenosis. (Circulation. 2004;110:790-795.)

Key Words: restenosis • stents • trials • angioplasty
Patients were considered eligible for randomization if they complained of angina pectoris or had exercise-induced ischemia in the presence of angiographically significant ISR in native coronary arteries. Patients with acute coronary syndromes or with severe infectious diseases were excluded. Other exclusion criteria were the presence of severe kidney failure (serum creatinine >2.2 mg/dL) or contraindications to the medication used in the present study (see below). The study was conducted according to the principles of the Declaration of Helsinki and approved by the institutional ethics committees. All patients had given their written informed consent for participation in this trial.

Randomization, Medication, and Coronary Procedures

After the presence of significant ISR had been diagnosed by coronary angiography, patients were randomly assigned to 1 of 3 study arms: placebo or usual-dose and high-dose sirolimus. Randomization was performed in a double-blind manner with the use of sealed envelopes containing the block randomization sequence for each participating center. The treatment protocol is summarized in Figure 1. All patients were pretreated for 2 days, followed by repeat percutaneous coronary intervention (PCI) on day 3. The difference between the usual- and high-dose sirolimus groups was in the intensified loading with a total of 24 mg of sirolimus in the high-dose (days 1 through 3) compared with 8 mg in the usual-dose group. After the intervention, a maintenance dose of 2 mg/d was given for 7 days in both groups. Double-blinding was achieved by the use of similar-appearing capsules containing either 2 mg of sirolimus or placebo for the respective treatment groups. Blood samples for the assessment of the sirolimus blood concentrations were taken at the time of the procedure and on the third day after the procedure before the drug administration of the day was received. The method for the determination of the sirolimus blood levels has been described in detail elsewhere. In addition, serum creatinine, cholesterol, triglycerides, and red and white blood cell and thrombocyte counts were analyzed before and at the end of the sirolimus treatment.

The protocol of repeat intervention for ISR has been described elsewhere. In brief, conventional angioplasty balloon catheters were used for repeat dilation to achieve a final diameter stenosis of <30% and Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 at the end of the procedure. Additional stents were placed in the presence of a suboptimal result or a large residual dissection (>5 mm in length) after angioplasty. The postprocedural antithrombotic regimen consisted of 75 mg of clopidogrel for at least 6 months after repeat intervention; 100 mg of aspirin twice daily was administered continuously.

Angiographic Evaluation

Qualitative and quantitative assessments in the core angiographic laboratory were performed before unblinding of the study. In-stent restenotic lesions were categorized with the use of the classification system suggested by Mehran and coworkers. Digital angiograms were analyzed offline with the automated edge-detection system (CMS V4.0, Medis Medical Imaging Systems). The analysis segment comprised the stent segment and the proximal and distal stent edges, defined as 5 mm proximal or distal to the stent. Matched views were selected for angiograms recorded before and immediately after the intervention and at follow-up. Each angiographic sequence was preceded by an intracoronary injection of nitroglycerin. The parameters obtained were minimum lumen diameter (MLD), vessel size, diameter stenosis, and diameter of the maximally inflated balloon. Acute lumen gain was calculated as the difference between MLD at the end of the intervention and before the balloon dilation. Late lumen loss was calculated as the difference in MLD noted between measurements after the procedure and at follow-up. Net gain was defined as the difference between MLD at follow-up and before balloon dilation.

Definitions and End Points of the Study

Patients without adverse events within the first 30 days after the procedure were considered eligible for repeat angiography at 6 months. Angiographic restenosis at follow-up, defined as diameter stenosis ≥50%, was the primary end point. Secondary end points were the combined incidence of death and myocardial infarction as well as target vessel revascularization (PCI or bypass surgery) during 1-year follow-up. The diagnosis of myocardial infarction was based on typical chest pain combined with either new pathological Q waves or an increase in creatine kinase to >3 times the upper limit of normal, with a concomitant increase in the MB isoenzyme. Creatine kinase was determined before and immediately after the procedure, every 8 hours for the first 24 hours after the procedure, and daily after that until discharge. Target vessel revascularization was performed in the presence of angiographic restenosis and symptoms or signs of ischemia. Adverse events were monitored throughout the follow-up period by a clinical visit at 6 months and an additional telephone interview at 1 year after the intervention. If patients reported cardiac symptoms during the telephone interview, at least a clinical and ECG follow-up examination were performed in the outpatient clinic or by the referring physician. All events were adjudicated and classified by an event-adjudication committee whose members were unaware of the patients' assigned treatment.

Statistical Analysis

The number of patients included in the present study was based on the sample size estimation for the primary end point of angiographic restenosis on the basis of a test-for-trend analysis. It was hypothesized that the incidence of restenosis is reduced by 25% with the usual dose and by 50% with the high dose of sirolimus. Accordingly, a sample size of 80 patients per group with repeat angiography at 6 months was calculated to detect these differences; we enrolled a total of 300 patients to accommodate patients in whom angiographic follow-up studies could not be obtained.

The main analysis was performed on an intention-to-treat basis, and the discrete variables are expressed as counts or percentages and compared by χ² or Fisher’s exact test, as appropriate. Continuous variables are expressed as mean±SD and are compared by means of the unpaired, 2-sided t test or ANOVA for >2 groups. Differences in restenosis rates were analyzed for statistical significance by the test for trend. Statistical significance was accepted for a value of P<0.05.

Results

Between October 2001 and February 2003, a total of 300 patients were randomized to receive the high (99 patients) or
usual (99 patients) dose of sirolimus or the placebo (102 patients). Clinical, angiographic, and procedural characteristics were comparable between the 3 groups, as shown in Table 1. Notably, one third of the patients had diabetes mellitus, and almost one half of the patients had already experienced a myocardial infarction.

The short course of treatment with oral sirolimus was well tolerated. The sirolimus blood levels on the day of the procedure were 10.0 ± 8.5 and 18.1 ± 5.2 µg/L in the usual- and high-dose sirolimus groups, respectively (P = 0.001). On the third day after the procedure, the blood levels were 6.6 ± 4.9 and 10.5 ± 5.0 µg/L in the usual- and high-dose sirolimus groups, respectively (P = 0.001). Significant changes in the serum creatinine, cholesterol, and triglyceride levels as well as red blood cell counts were not observed. In the high-dose sirolimus group, the white blood cell counts were significantly reduced at the end of the sirolimus treatment (cell count before treatment: 7.0 ± 1.9 × 10³, 7.0 ± 2.0 × 10³, and 6.9 ± 1.6 × 10³/µL; P = 0.89; cell count at the end of treatment: 5.5 ± 1.4 × 10³, 6.4 ± 1.8 × 10³, and 7.1 ± 2.0 × 10³/µL; P < 0.001 for the high-dose, usual-dose, and placebo groups, respectively). Similarly, the thrombocyte counts were significantly lower in the high-dose group at the end of the sirolimus treatment (cell count before treatment: 220 ± 65 × 10³, 230 ± 68 × 10³, and 216 ± 75 × 10³/µL; P = 0.37; cell count at the end of treatment: 199 ± 69 × 10³, 240 ± 72 × 10³, and 266 ± 88 × 10³/µL; P < 0.001 for the high-dose, usual-dose, and placebo groups, respectively). There were no clinical consequences of either leukopenia or thrombocytopenia. The medication was discontinued in a total of 8 patients because of suspected allergic drug reaction (1 placebo patient and 2 high-dose patients), infectious complications (1 usual-dose patient with bacterial joint infection and 1 high-dose patient with otitis), a considerable drop in hemoglobin (1 usual-dose patient), frequent vomiting (1 usual-dose patient), and extensive diarrhea (1 high-dose patient).

Repeat angiography was performed in 259 of 294 eligible patients (88.4%) at a median time interval of 206 days (25%
The angiographic results are summarized in Table 2. Compared with the placebo group, the angiographic restenosis rate was reduced significantly, by 48%, in the high-dose sirolimus group (P=0.005). Figure 2 illustrates the restenosis rates in each group. Consequently, the late lumen loss was lowest (P=0.047) and the MLD highest (P=0.013) in the high-dose sirolimus group. Cumulative distribution curves for the degree of percent diameter stenosis at follow-up are demonstrated in Figure 3. A significant correlation between the sirolimus blood level at the time of intervention with late lumen loss at follow-up is shown in Figure 4. With increasing blood levels of sirolimus, a lower late lumen loss at follow-up was observed (r=0.3; P<0.001). The sirolimus blood levels on day 3 showed a weaker correlation with late lumen loss at follow-up (r=0.21, P=0.018).

Major adverse cardiac events at 30 days, including death, myocardial infarction, or the need for repeat intervention, occurred in 2%, 3%, and 2% of patients in the placebo, usual-dose, and high-dose sirolimus groups, respectively (P=0.85). One-year clinical follow-up was completed in 293 of 300 randomized patients (97.8%). Table 3 summarizes the clinical outcome at 1 year. The combined rate of death or myocardial infarction at 1 year was 1.0%, 3.0%, and 2.0% in patients randomized to the placebo, usual-dose, and high-dose groups, respectively (P=0.59). Table 4 summarizes the causes of death in more detail. Target vessel revascularization because of restenosis was necessary in 26 patients (25.5%) of the placebo group, in 24 patients (24.2%) in the normal-dose group, and in 15 patients (15.2%) of the high-dose group (P=0.08; Figure 2).

**Discussion**

This randomized, double-blind, and placebo-controlled trial was performed to assess the impact of an oral, short-term administration of sirolimus for the prevention of restenosis after PCI in patients at high risk for recurrent restenosis. The trial demonstrates that short-term administration of sirolimus over a total of 10 days, including 2 days with an intensified loading dose before the intervention, results in a significant reduction of angiographic restenosis after treatment of ISR. Furthermore, the study reveals a significant correlation of the sirolimus blood level at the time of intervention with late lumen loss at follow-up.

Sirolimus, a macrolide immunosuppressant with anti-inflammatory and antiproliferative capacities, is a fermentation product of *Streptomyces hygroscopicus*.

### Table 2. Angiographic Results at Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Placebo (90 Patients)</th>
<th>Usual-Dose Sirolimus (83 Patients)</th>
<th>High-Dose Sirolimus (86 Patients)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum lumen diameter, mm</td>
<td>1.53±0.61</td>
<td>1.37±0.69</td>
<td>1.66±0.62</td>
<td>0.013</td>
</tr>
<tr>
<td>Vessel size, mm</td>
<td>2.70±0.52</td>
<td>2.54±0.63</td>
<td>2.65±0.54</td>
<td>0.173</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>43.7±18.4</td>
<td>45.8±21.5</td>
<td>38.1±17.7</td>
<td>0.028</td>
</tr>
<tr>
<td>Late lumen loss, mm</td>
<td>0.60±0.56</td>
<td>0.72±0.70</td>
<td>0.49±0.54</td>
<td>0.048</td>
</tr>
<tr>
<td>Net lumen gain, mm</td>
<td>0.68±0.61</td>
<td>0.50±0.69</td>
<td>0.74±0.51</td>
<td>0.028</td>
</tr>
<tr>
<td>No. of patients with restenosis</td>
<td>38</td>
<td>32</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Incidence of restenosis (CI), %</td>
<td>42.2 (28.1–49.0)</td>
<td>38.6 (13.3–30.9)</td>
<td>22.1 (32.0–52.4)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Figure 2. Bar graph demonstrating angiographic restenosis rates at 6 months and clinical restenosis rates at 1 year (need for target vessel revascularization [TVR], repeat coronary intervention, or bypass surgery).

Figure 3. Percent diameter stenosis in treatment groups.
been shown in the series of SIRIUS trials (SIRoIImUS-eluting Bx velocity balloon-expandable stent trial; SIRIUS, 7 and E-SIRIUS8) resulted in widespread use of this device in clinical and anatomic situations, many of which have not been specifically studied. However, at present, cost constraints and lack of incremental reimbursement may limit the use of drug-eluting stents in daily practice in many countries. Furthermore, the usefulness of sirolimus-eluting stents for the prevention of recurrent restenosis has not been documented in patients with ISR.

Two nonrandomized studies with oral sirolimus in small patient groups have been conducted.12,13 In the first study, by Brara and coworkers,12 no clinical benefit was observed in 22 patients with ISR. In the second small registry, a trend toward a lower restenosis rate was observed in de novo lesions, particularly in patients with higher sirolimus blood levels.13 In both studies, the treatment duration with oral sirolimus was 1 month, and the sirolimus dosing was comparable with that of the usual-dose group of the present trial, but the treatment was started after and not before the coronary procedure. The importance of the pretreatment to ensure therapeutic sirolimus blood levels at the time of the procedure was a central issue in this trial. We hypothesized that the sirolimus levels at the time of the procedure will have a major impact on restenosis prevention. Therefore, we included a treatment group with an intensified sirolimus loading before the procedure but a maintenance dose identical to that of the usual-dose group. This concept with an intensified oral sirolimus loading resulted in significant improvements in the angiographic parameters of restenosis; eg, the binary restenosis rate was reduced by 48% with the intensified loading and by 9% with the usual-dose sirolimus loading compared with placebo. Furthermore, a significant correlation between the sirolimus blood levels on the day of the procedure and the late lumen loss was observed. These findings, in combination with the weaker correlation between the sirolimus blood levels at day 3 and the late lumen loss, may imply that the inhibition of the initiating steps in neointima proliferation by sirolimus is critical for restenosis prevention.

The clustering of 5 patients in the 2 sirolimus groups who died during the follow-up period is of some concern in this trial, which was not powered to address mortality. In the treatment of cardiac transplant vasculopathy, the long-term administration of sirolimus was not associated with an increased mortality.4 Although it seems unlikely that the short, 10-day treatment with sirolimus is the cause for the rather late-occurring deaths, further studies may be needed to rule out a potential hazardous impact of this treatment regimen before this strategy is adopted in clinical routine.

At the end of the short sirolimus treatment, the leukocyte and thrombocyte counts demonstrated a small but significant decrease in the high-dose group, but these did not result in any clinical manifestations. Overall, the systemic sirolimus treatment was well tolerated, and there was a low need for termination of treatment, which may be explained by the short treatment duration of only 10 days. Higher rates and more severe side effects have been reported in previous studies in which the treatment was given for at least 30 days.

**Limitations of the Study**
The highest late lumen loss was observed in the usual-dose sirolimus group, and a possible stimulatory effect of this dose cannot be ruled out. Conversely, the late lumen loss of 0.60 mm in the placebo group is slightly lower of that of 0.72 mm reported in a previous randomized trial. This may account for the difference in the late lumen loss observed between the usual-dose sirolimus and the placebo group being more evident.

It is unknown whether the present findings will be maintained during more prolonged follow-up. Furthermore, the optimal dosing, the need for pretreatment, and duration of oral sirolimus for the prevention of restenosis have not yet been determined. Although the present results support the need for an intensified pretreatment, we cannot distinguish between the need for an increased initial sirolimus dose or a prolonged pretreatment to reduce restenosis. The present 10-day treatment duration was used with the intent to approximate the treatment duration of the fast-release sirolimus.

**Table 3. Clinical Outcome at 1 Year**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (102 Patients)</th>
<th>Usual-Dose Sirolimus (99 Patients)</th>
<th>High-Dose Sirolimus (99 Patients)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, %</td>
<td>0</td>
<td>3.0</td>
<td>2.0</td>
<td>0.23</td>
</tr>
<tr>
<td>Myocardial infarction, %</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
<td>0.23</td>
</tr>
<tr>
<td>Death or myocardial infarction, %</td>
<td>1.0</td>
<td>3.0</td>
<td>2.0</td>
<td>0.59</td>
</tr>
<tr>
<td>Target vessel revascularization, %</td>
<td>25.5</td>
<td>24.2</td>
<td>15.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Cumulative event rate, %</td>
<td>27.5</td>
<td>29.3</td>
<td>18.2</td>
<td>0.15</td>
</tr>
</tbody>
</table>
The potential usefulness of drug-eluting stents for the treatment of patients with ISR has been evaluated in 2 recent small registries. However, additional randomized studies are needed to investigate the efficacy and cost-effectiveness of various interventional treatments for ISR, including intracoronary brachytherapy, drug-eluting stents, and the systemic administration of sirolimus.

In conclusion, the oral administration of sirolimus with an intensified loading regimen in patients with ISR resulted in significant improvements in the angiographic parameters of restenosis after repeat coronary intervention. The improved angiographic outcome translated into a trend for a reduced need for target vessel revascularization at 1-year clinical follow-up in the intensified sirolimus loading group. The sirolimus concentration in the blood at the time of the procedure correlated significantly with the late lumen loss at follow-up, which may imply that the inhibition of the initiating steps in neointima proliferation by sirolimus is critical for restenosis prevention.

Appendix

The organization of the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial was as follows.

Steering Committee
A. Schoimid (chairman), A. Kastrati, J. Dirschinger.

Data Coordinating Center

Angiographic Core Laboratory

OSIRIS Study Sites and Investigators

TABLE 4. Summary of Patients Who Died During Follow-Up

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Group</th>
<th>Procedure to Death, d</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>Usual-dose</td>
<td>27</td>
<td>Cerebral bleeding</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>Usual-dose</td>
<td>173</td>
<td>Septicemia after orthopedic surgery</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>Usual-dose</td>
<td>215</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>High-dose</td>
<td>14</td>
<td>Sudden death after additional PCI</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>High-dose</td>
<td>66</td>
<td>Cardiogenic shock with multiorgan failure</td>
</tr>
</tbody>
</table>

Acknowledgment

This study was supported by a research grant from the Deutsches Herzzentrum, Klinik an der Technischen Universität, Munich, Germany (No. 04-03).

References

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_Circulation._ 2004;110:790-795; originally published online August 9, 2004; doi: 10.1161/01.CIR.0000138935.17503.35

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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