Five-Year Clinical Follow-Up After Intracoronary Radiation Results of a Randomized Clinical Trial

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Background—Several clinical trials indicate that intracoronary radiation is safe and effective for treatment of restenotic coronary arteries. We previously reported 6-month and 3-year clinical and angiographic follow-up demonstrating significant decreases in target lesion revascularization (TLR) and angiographic restenosis after γ radiation of restenotic lesions. The objective of this study was to document the clinical outcome 5 years after treatment of restenotic coronary arteries with catheter-based iridium-192 (192Ir).

Methods and Results—A double-blind, randomized trial compared 192Ir to placebo sources in patients with restenosis after coronary angioplasty. Over a 9-month period, 55 patients were enrolled; 26 were randomized to 192Ir and 29 to placebo. At 5-year follow-up, TLR was significantly lower in the 192Ir group (23.1% versus 48.3%; P=0.05). There were 2 TLRs between years 3 and 5 in patients in the 192Ir group and none in patients in the placebo group. The 5-year event-free survival rate (freedom from death, myocardial infarction, or TLR) was greater in 192Ir-treated patients (61.5% versus 34.5%; P=0.02).

Conclusions—Despite apparent mitigation of efficacy over time, there remains a significant reduction in TLR at 5 years and an improvement in event-free survival in patients treated with intracoronary 192Ir. The early clinical benefits after intracoronary γ radiation with 192Ir seem durable at 5-year clinical follow-up. (Circulation. 2002;105:2737-2740.)

Key Words: restenosis ■ angioplasty ■ stents ■ radioisotopes

Restenosis continues to be the Achilles heel of catheter-based vascular procedures.1,2 There is extensive evidence indicating intracoronary brachytherapy is effective in reducing restenosis.3–14 We previously reported the 6-month and 3-year results demonstrating benefit from γ radiation.5,15 However, the possibility of late radiation-associated adverse effects such as accelerated vascular disease, aneurysm formation, late thrombosis, and late lumen loss is of concern.16–21 The objective of this study was to document the clinical outcomes 5 years after treatment of restenotic stented coronary arteries with catheter-based iridium-192 (192Ir).

Methods

The Scripps Coronary Radiation to Inhibit Proliferative Post-Stenting (SCRIPPS) trial is a double-blind randomized trial comparing 192Ir with placebo sources. The methods have been described in detail previously.5 This clinical trial was approved by the institution’s Human Subjects and Radiation Safety Committees. Patient inclusion criteria required a target lesion in a restenotic coronary artery that either already contained a stent or was a candidate for stent placement. If the lesion was not already stented, single or (if required) tandem coronary stenting (Johnson & Johnson Interventional Systems) was performed. If stents had been placed previously, redilatation was undertaken, and often additional stents were placed within the original stent to optimize the angiographic result. In all cases, high-pressure (≥18 atm) balloon dilations were performed in an attempt to achieve a 0% residual stenosis within the stented segment. Patients were then randomly assigned to receive a 0.76-mm (0.03-inch) ribbon (Best Industries) containing sealed sources of either 192Ir or placebo. The study ribbon was left in place for 20 to 45 minutes, as required to administer the prescribed dose of 800 to 3000 cGy to the adventitial border.6

Patients were requested to return for coronary angiography at 6 months and again at 3 years. All living patients were contacted or after the 5-year anniversary of their index procedure. Medical records were obtained from each patient’s primary treating physician along with copies of hospital records from all admissions and procedures. When necessary, the county coroner’s office was contacted to obtain data regarding the cause and date of the patient’s death. Two patients who were initially lost to follow-up were located by a commercial service (1-800-US-SEARCH).

Target lesion revascularization (TLR) was defined as coronary angioplasty or surgical bypass of the target vessel attributable to the presence of ≥50% diameter stenosis of a target lesion. The target lesion was defined as the stented segment in addition to the stent...
TABLE 1. Baseline Clinical and Angiographic Characteristics of 55 Patients With Restenosis Assigned to Receive $^{192}$Ir or Placebo

<table>
<thead>
<tr>
<th></th>
<th>$^{192}$Ir (n=26)</th>
<th>Placebo (n=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69.8±9.7</td>
<td>68.8±10.8</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>73</td>
<td>76</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>27</td>
<td>41</td>
<td>0.4</td>
</tr>
<tr>
<td>Unstable angina, %</td>
<td>42</td>
<td>55</td>
<td>NS</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>38</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>65</td>
<td>69</td>
<td>NS</td>
</tr>
<tr>
<td>Previous restenoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.1±1.4</td>
<td>2.0±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;1%</td>
<td>52</td>
<td>55</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;2%</td>
<td>23</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>In-stent restenosis</td>
<td>62</td>
<td>62</td>
<td>NS</td>
</tr>
<tr>
<td>No. of stents in target lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td>45</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>55</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>46.7%</td>
<td>48.9%</td>
<td>NS</td>
</tr>
<tr>
<td>Location of target lesion, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saphenous vein grafts</td>
<td>23</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>LAD</td>
<td>31</td>
<td>38</td>
<td>NS</td>
</tr>
<tr>
<td>Ostial</td>
<td>31</td>
<td>41</td>
<td>NS</td>
</tr>
<tr>
<td>Aorto-ostial</td>
<td>12</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>12.89±7.05</td>
<td>11.86±6.77</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion length &gt;10 mm, %</td>
<td>58</td>
<td>45</td>
<td>NS</td>
</tr>
</tbody>
</table>

Plus-minus values are mean±SD. All other values are percentages of patients.

margin 5 mm proximal and distal to the radioactive or placebo sources. Thus, TLR included revascularization of both in-stent restenosis and restenosis at the stent or source margins attributable to edge effect. Target vessel revascularization (TVR) included revascularization of the target lesion or a segment outside the target lesion but within the same vessel. Non-TLR was defined as revascularization of an epicardial vessel that did not contain the target lesion. Myocardial infarction (MI) was defined as an elevation of the MB fraction of creatinine kinase to a value 3 times the upper limit of the normal range.

Categorical data were compared with the use of $\chi^2$ or Fisher’s exact test except for the composite clinical end point, which was analyzed by means of Kaplan-Meier survival analysis, with differences between the 2 treatment groups compared with the use of a Mantel-Cox test of significance.

Results

Between March 24 and December 22, 1995, 55 patients were enrolled; 26 were randomized to $^{192}$Ir and 29 to placebo. Baseline clinical and angiographic factors (Table 1) were similar in the two groups, although there was a trend toward more patients with diabetes in the placebo arm. In-stent restenosis was present in 62% of both the $^{192}$Ir and placebo groups.

Clinical follow-up (Table 2) was obtained on or after the 5-year anniversary following the index procedure in 100% of the living patients in the both treated and the placebo groups. The mean time from index study procedure to clinical follow-up was similar in $^{192}$Ir and placebo groups (61.1 versus 60.8 months; $P=0.77$). Follow-up times ranged from 60 to 67 months in patients in the $^{192}$Ir group and 60 to 62 months in patients in the placebo group.

At 5-year follow-up, TLR occurred in a total of 6 patients (23.1%) in the $^{192}$Ir group compared with 14 patients (48.3%) in the placebo group ($P=0.05$). There were 2 TLR procedures in the $^{192}$Ir group between years 3 and 5. The first patient presented at 54 months with recurrent angina, which had previously been quiescent, and underwent angiography followed by balloon angioplasty at the index site. Initial quantitative angiographic follow-up at 6 months revealed the index lesion had a minimal luminal diameter (MLD) of 2.76 mm and a diameter stenosis of 22%. By 36 months, this lesion had progressed to a 41.2%-diameter stenosis with an MLD of 1.74 mm. At the time of the patient’s TLR at 54 months, the diameter stenosis had additionally increased to 58.2%, with a decrease in MLD to 1.65 mm. The restenotic region was focal and well within the stent borders. The second patient presented at 55 months with one episode of chest pain and underwent angiography and balloon angioplasty to the index lesion. Earlier angiographic follow-up had revealed some late lumen loss between 6 and 36 months, with the diameter stenosis increasing from 24% (MLD 3.27 mm) to 55.1% (MLD 1.66 mm). At the time of the patient’s TLR at 55 months, the lesion had not additionally progressed by quantitative coronary angiography; the diameter stenosis was 54.4% and MLD was 1.77 mm. This lesion was also focal and within the stented region. Both of these patients clearly sustained their late restenosis within the previous $^{192}$Ir region. Therefore, these late failures were not attributable to edge effect or geographic miss. One TLR occurred in a patient in the placebo group at 60 months who had undergone a previous TLR by 3-year follow-up.
In the 192 Ir group, 1 patient whose index vessel was the left anterior descending, presented at 45 months with chest pain and had progression of left main disease (which was distant from the radiation field), which was treated with bypass surgery. The 192 Ir region was unchanged. In the placebo group, there were 2 patients who underwent non-TVR. One patient whose vein graft to his circumflex artery was his index vessel underwent stenting of his native circumflex at 59 months. Another patient in the placebo cohort presented at 40 weeks with unstable angina. His index vessel had been the right coronary artery, and his culprit vessel was the diagonal branch, which was stented.

Discussion

This study reports the longest follow-up of a randomized, double-blinded, placebo-controlled trial of γ radiation versus placebo for the treatment of coronary restenosis. Numerous studies have demonstrated the early safety and efficacy of both γ and β radiation.\(^{3-14}\) To date, however, data regarding outcomes beyond 1-year follow-up are limited.\(^{15,22}\) We sought to address some of the concerns regarding long-term safety and efficacy of this relatively new therapy, including the possibility of late luminal loss, accelerated disease in nontreated vessels, aneurysms, and perforations.

In our previous 3-year follow-up analysis, we evaluated the MLD of the target lesion in patients who had not undergone a TLR by 6 months. Between the index procedure and 6 months there was some decrease in mean MLD in both the placebo and 192Ir groups. Between 6 months and 3 years, however, changes in MLD were slightly different. The placebo cohort had no additional late loss (mean MLD, 2.35 mm at 6 months versus 2.35 mm at 36 months), whereas in the 192Ir group we found a decrease in mean MLD (2.49 mm at 6 months versus 2.12 mm at 36 months).

An important objective of our 5-year follow-up was to determine if there were additional decreases in MLD that might result in an increase in late revascularization procedures.

We found 2 late TLR procedures between 3 and 5 years in the 192Ir group. In 1 patient, there was clear progression of the stenosis. In the second case, there was no apparent decrease in the diameter stenosis or MLD. Both of these treated patients had a clinical revascularization event. In contrast, no late target-lesion revascularizations were observed in placebo patients. Therefore, we found some loss in the clinical efficacy of radiation over time. At 6 months, the there was a 74% reduction in TLR (44.8% versus 11.5%; \(P=0.01\)), which decreased to a 68% reduction at 36 months (48.3% versus 15.4%; \(P < 0.01\)) and a 48% reduction (48.3% versus 23.1%; \(P=0.05\)) at 5 years (Figure 2). It should be noted, however, that although there is some attrition in efficacy over time, significant differences in TLR persist over the entire follow-up period. An important finding at late follow-up was a reduction in the composite end point of death, MI, or TLR (65.5% versus 38.5%; \(P=0.04\)).

At 5 years there was no longer a significant difference in either TVR or the composite end point of death, MI, or TVR. However, there were trends favoring the 192Ir cohort. One must consider that before receiving brachytherapy, most of the patients in our study had repeated episodes of restenosis and it took 5 years of follow-up for the end point of TVR to lose statistical significance. In some patients, therefore, vascular radiation may delay instead of eliminate the restenotic process, but this may still result in an improved quality of life.

**Figure 1.** Kaplan-Meier curves for event-free survival in 192Ir and placebo groups. Event-free survival was defined as survival without MI or repeated revascularization of target lesion. The 2 curves begin to separate at \(~3\) months, and the differences persist throughout the follow-up period.

**Table 1.** 5-year clinical outcomes for 192Ir and placebo groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Event-Free Survival</th>
<th>TVR</th>
<th>TVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>72.4% (0.15)</td>
<td>65.5% (0.13)</td>
<td>25% (0.12)</td>
</tr>
<tr>
<td>192Ir</td>
<td>80.8% (0.02)</td>
<td>38.5% (0.04)</td>
<td>15.4% (0.05)</td>
</tr>
</tbody>
</table>

MI in 192Ir group was lower in patients than placebo group (38.5% versus 65.5%; \(P=0.04\)). Life-table analysis of this composite end point is displayed in Figure 1. The 2 curves begin to separate at \(~3\) months, and the differences persist throughout the follow-up period. Significantly better event-free survival over the 5-year period was found in treated compared with placebo patients (61.5% versus 34.5%; \(P=0.02\)).

There was a trend toward less TVR in the 192Ir versus placebo group, 10 patients (38.5%) versus 17 patients (58.7%) \(P=0.13\). The composite of death, MI, or TVR also trended lower in the 192Ir group, 14 patients (53.8%) versus 21 patients (72.4%) \(P=0.15\).

The non-TLR and non-TVR rates were low in both groups. In the 192Ir group, 1 patient whose index vessel was the left anterior descending, presented at 45 months with chest pain and had progression of left main disease (which was distant from the radiation field), which was treated with bypass surgery. The 192Ir region was unchanged. In the placebo group, there were 2 patients who underwent non-TVR. One patient whose vein graft to his circumflex artery was his index vessel underwent stenting of his native circumflex at 59 months. Another patient in the placebo cohort presented at 40 weeks with unstable angina. His index vessel had been the right coronary artery, and his culprit vessel was the diagonal branch, which was stented.

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Our cohort of patients had advanced coronary disease with a large percentage sustaining death, MI, or any revascularization by 5 years. However, patients who received intracoronary $^{192}$Irradiation had fewer of these events compared with patients in the placebo group (57.7% versus 86.2%; $P=0.02$), again demonstrating the efficacy of this therapy.

Over the 5-year follow-up period, there were a total of 5 deaths among the 26 patients in the $^{192}$Ir group (19.2%) and 9 deaths among the 29 patients in the placebo group (31%). Although this number of late deaths raises concern, it should be noted that many of our patients were elderly and had diabetes mellitus, previous MI, or depressed ventricular function in addition to their restenotic coronary disease. The number of cardiac deaths was nonsignificantly lower in treated patients versus patients in the placebo group (11.5% versus 20.6%).

One of the concerns with intracoronary brachytherapy is the unknown long-term effects of radiation on coronary artery architecture, aneurysm formation, progression of disease in nearby vessels, or other safety issues. In this small series we did not document any apparent late thrombosis. There were 2 late sudden deaths in the $^{192}$Ir group that may have been attributable to late thrombosis; however, there were also 3 sudden deaths in patients in the placebo group. At 5-year follow-up, we found no increase in non-TVR in patients in the $^{192}$Ir group compared with patients in the placebo group (30.8% versus 34.5%; $P=0.77$).

Study Limitations

The major limitation of this study was its small sample size. However, our conclusions are supported by obtaining 100% follow-up of all living patients at 5 years or longer. Additionally, there were more diabetic patients in the placebo group than in the treatment arm, possibly contributing to higher event rates in this cohort. There were no mandated angiograms after year 3, and all subsequent events were clinically driven; thus, we do not know if there was any subclinical coronary pathology in the treated group. However, there were no unexpected adverse angiographic findings in the 2 patients who underwent late clinically driven cardiac catheterization, and there were less cardiac deaths in the treated cohort.

Conclusions

With 100% clinical follow-up 5 years after study entry, the clinical efficacy of $^{192}$Ir radiation seems durable. In $^{192}$Ir-treated patients, TLR was reduced by 74% at 6-month, 68% at 3-year, and 48% at 5-year follow-up. There were no long-term safety issues. At the 5-year time point, vascular brachytherapy continues to be an effective therapy for in-stent restenosis.

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References

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