Review of Intracoronary Radiation for In-Stent Restenosis

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Vascular Brachytherapy using beta and gamma radiation is the standard care for patients with in-stent restenosis (ISR). The reported incidence of ISR varies from 7-37% of patients who undergo bare metal stent implantation and is dependent on patient characteristics, lesion morphology, and procedural technique.[1] The recurrence rate after treatment for ISR varies among reported series but remains high, ranging from 35-85%, regardless of treatment modalities, including balloon angioplasty, rotational or directional atherectomy, excimer laser ablation, re-stenting and cutting balloon. The diffuse pattern of ISR (> 10 mm) is associated with even higher rates of recurrence and presents a therapeutic challenge.[2-4] Serial intravascular ultrasound (IVUS) studies have demonstrated that ISR results primarily from neointimal tissue hyperplasia distributed either focally or diffusely over the entire length of the stent.[5-6]

Recently, new stent designs and the use of drug-eluting stents have shown promise in decreasing the overall incidence of in-stent restenosis. Yet even for the Sirolimus eluting stent, the reported restenosis in diabetes, small vessel, and long lesions range from 15-18%. ISR continues to be a clinical problem.[7] This review summarizes the clinical trials in vascular brachytherapy using beta or gamma radiation for the treatment of ISR with an emphasis on lessons learned from these trials and its role in the era of drug-eluting stents.

The GAMMA Trials. The only gamma emitter used in clinical trials for ISR is ^{192}Iridium (^{192}Ir) using the Checkmate system (Cordis Corporation, Warren, New Jersey) with different trains of seeds ranging from 6-23 (Best Industry, Springfield, Virginia).

Scripps Coronary Radiation to Inhibit Proliferation Post Stenting (SCRIPPS). SCRIPPS was the first randomized trial to determine the safety and efficacy of intracoronary gamma radiation given as adjunctive therapy to stents. In this study, a total of 26 of 54 patients were randomized to receive ^{192}Ir (8-30 Gy, dosimetry guided by IVUS) utilizing a ribbon (19-35 mm) delivered in a non-centered, closed-end lumen catheter at the treatment site (dwell time: 20-45 minutes). Only 35 patients in this cohort were patients with ISR. This study demonstrated that at six-months the angiographic restenosis rate was reduced with radiation (17% vs. 54%; $p < 0.01$). At three years, these results remained consistent (33% vs. 64.3%; $p < 0.05$). Sub-analysis of the lumen diameter for patients who did not have further intervention demonstrated minimal reduction of the MLD of the irradiated segments versus control at 3 years. There were no evident clinical complications resulting from the radiation treatment, and clinical benefits were maintained at three years with a significant reduction in the need for target lesion revascularization ($p = 0.004$). A subgroup analysis for the 35 patients with ISR has shown a 70% reduction of the recurrence rate in the irradiated group versus the placebo group.[8] Recent five-year follow-up of this cohort of subjects showed continued benefit of intracoronary radiation, with improvement in TLR and event-free survival.[9]

Washington Radiation for In-Stent Restenosis Trial (WRIST). WRIST is a series of studies that were designed to evaluate the effectiveness of radiation therapy for

ISR.[10] The gamma radiation in these studies is composed of ribbon with different trains of radioactive (^{192}Ir) seeds, which is inserted manually into a closed-end lumen catheter. In the initial study, 130 patients (100 patients with native coronaries and 30 patients with vein grafts) with ISR lesions (up to 47 mm in length) were blindly randomized to treatment with either placebo or 15 Gy of ^{192}Ir at 2 mm from the source of the vessel wall. At six months, clinical and angiographic follow-up showed a dramatic reduction of the restenosis rate between the irradiated group and the control group, 19% vs. 58% respectively ($p = 0.0001$). There was a 79% reduction in the need for revascularization and a 63% reduction in major adverse cardiac events (death, Q-wave myocardial infarction or target vessel revascularization) in the irradiated group compared to control. Intravascular ultrasound sub-analysis demonstrated 53% of lesions from the irradiated group had increased luminal dimensions and regression of neointimal tissue at 6 months. Between 6 and 48 months, an interesting observation was noted; IRT compared to placebo patients had more target lesion revascularization (18% vs. 2%; $p = 0.001$) and target vessel revascularization (19% vs. 3%; $p = 0.003$). This likely reflects an initial freezing of neointimal growth with IRT, with diminished effectiveness over time. However, at 4-year clinical follow-up, the IRT cohort continued to have markedly lower MACE rates when compared with controls (40% vs. 65%; $p = 0.005$). The WRIST study is considered to be a landmark in establishing gamma radiation for the treatment of ISR.

LONG WRIST. LONG WRIST was a randomized trial involving 120 symptomatic patients with diffuse, in-stent restenotic lesions 36 mm to 80 mm (mean stent length: 70 mm) who received either a ribbon bearing ^{192}Ir seeds or placebo seeds delivered to the target site via a non-centered, closed-lumen catheter. The radiation dosage consisted of 14-15 Gy at a 2 mm distance from the center of the source. Quantitative coronary angiography at six months disclosed rates of restenosis of 32% in the irradiated group and 71% in the control group within the stented segment only ($p = 0.0002$). Rates of restenosis considering only the segment containing the lesion were 46% and 78%, respectively ($p = 0.03$). The 6-month rates of major adverse cardiac events were 38.3% and 61.7%, respectively ($p = 0.01$), with most of the significant difference accounted for by the TLR component; the rates for which were 30% and 60%, respectively ($p = 0.001$). The rate of late total occlusion at any time during the follow-up was 15% of irradiated patients and 6.7% of controls.

LONG WRIST High Dose. LONG WRIST High Dose was a registry of 120 patients with similar entry criteria to LONG WRIST. In comparison to LONG WRIST, a higher radiation dose was prescribed with 18 Gy delivered at a 2 mm distance from the center of the source. The second 60 consecutive patients of LONG WRIST High Dose received prolonged antiplatelet therapy (clopidogrel or ticlopidine) for 6 months instead of one month. Baseline clinical and angiographic details were similar in both study groups. At 6-month follow-up, major adverse cardiac events were reduced by 39% in the high dose group (23% vs. 38%; $p = 0.11$) compared to LONG WRIST. Patients in the LONG WRIST High Dose group with 6 months of antiplatelet therapy had a strikingly low rate of TVR (17%) and MACE (17%) compared to one month of antiplatelet therapy in the LONG WRIST groups.

IVUS analysis post-intervention and at 6-month follow-up was performed in 25 patients from LONG WRIST High Dose and in 30 IRT and 34 placebo patients from LONG WRIST.11 Stent length was longer in LONG WRIST High Dose than in placebo or treated patients in LONG WRIST ($p = 0.006$ and $p = 0.013$, respectively). At follow-up, the minimum lumen area was largest in the LONG WRIST High Dose patients (4.0 ± 1.4 mm^2); areas were 2.9 ± 1.0 mm^2 in IRT patients and 1.9 ± 1.1 mm^2 in placebo patients in LONG WRIST ($p < 0.005$ for all comparisons). The clinical and serial IVUS analysis showed that IRT reduces recurrent in-stent neointimal hyperplasia in diffuse ISR lesions; furthermore diffuse lesions may require higher radiation doses and prolonged antiplatelet therapy to maintain the efficacy seen in focal lesions and to minimize recurrent clinical events at 6 months.

Washington Radiation for In-Stent restenosis Trial for Saphenous Vein Grafts (SVG WRIST). SVG WRIST was a Food and Drug Administration (FDA) approved, double-blind, multicenter, randomized trial in patients post coronary bypass surgery with diffuse ISR of saphenous vein grafts (SVG).[12] SVG WRIST was the first study to examine the effects of gamma radiation therapy on patients with ISR in bypass grafts. One hundred and twenty patients with diffuse ISR in SVG underwent PTCA, laser ablation or rotational atherectomy, and/or additional stents. After the intervention, a non-centered, closed-end lumen catheter was positioned at the treated site, and patients were randomly assigned to a ribbon with either ^{192}Ir or with non-radioactive seeds both delivered by hand. Different ribbon lengths of 6, 10, and 14 seeds with a mean radiation length of 34 ± 22 mm were used to cover lesions < 47 mm in length. The prescribed radiation doses were 14 or 15 Gy to a 2 mm radial distance from the center of the source for vessels with a diameter of 4 mm and 15 Gy at 2.4 mm for vessels > 4 mm in diameter. The patients with restenosis at follow-up were eligible to receive radiation if initially randomized to placebo. The closed-end lumen catheter with either the active or the placebo seeds was delivered successfully to all patients. A mean dwell time of 21.1 ± 4.8 minutes was well tolerated in irradiated patients. At 30 days, there were no adverse events related to the radiation therapy. At 6 months, the restenosis rate was significantly lower in the irradiated group compared to control (15% vs. 43%; $p = 0.004$). The need for repeat intervention at the treatment site was significantly reduced by 79% in the irradiated group compared to control (10% vs. 48%; $p < 0.001$), and the overall major cardiac events were reduced in the irradiated group (20% vs. 55%; $p < 0.001$). The rate of late thrombosis in the irradiated group was 1.7% versus 6.7% in the control (p = NS), and there was no excess of edge effect in the irradiated group when compared to the control.

IVUS analysis post-intervention and at 6-month follow-up was performed. In the irradiated patients, there was no change in stent, lumen, or intimal hyperplasia (IH) area or volume, while in the control patients there was an increase in intra-stent IH area ($p < 0.0001$) resulting in a decrease in lumen area ($p < 0.001$). Conventional treatment of ISR in bypass grafts is associated with a high recurrence rate. The SVG WRIST study demonstrated that catheter based gamma radiation therapy for ISR in bypass grafts is safe and effective in reducing the overall restenosis rate and the need for repeat revascularization.

Examination of records of 1,142 patients (230 in SVG and 912 in native coronaries) from the WRIST series of studies detected that gamma IRT in saphenous vein grafts had similar outcomes to native coronaries with equivalent rates of angiographic restenosis (22% vs. 29%; p = NS) and target vessel revascularization (27% vs. 23%; p = NS) at 6-month follow-up.

GAMMA-1. GAMMA-1 was a multicenter, randomized, double blind trial studying the effects of hand-delivered ^{192}Ir ribbon using intravascular ultrasound to guide dosimetry (dose range 8-30 Gy) in 252 patients with ISR. Six-month angiographic results revealed significant reductions in the in-stent (22% vs. 52%) and in-lesion (33% vs. 56%; p = 0.006) angiographic restenosis rates of the radiation arm versus control. Sub-analysis for lesion length demonstrated a 70% reduction in the angiographic restenosis rate for lesions < 30 mm in length versus 48% for 30-45 mm lesions.[13] In addition, edge effect was noted in patients who did not have enough coverage of the lesion by the radioactive seeds. Clinical events demonstrated a reduction in the TLR rate from 42% to 24%. However, the rate of death (3% versus 0.8%) and the rate of acute MI (12% versus 6%) were higher in the irradiated group versus control. These complications were related in part to the late thrombosis phenomenon.

GAMMA-2. GAMMA-2 was a registry of 125 patients who were treated for the same inclusion/exclusion criteria as GAMMA-1 but with a fixed dosimetry of 14 Gy at 2 mm from the center of the source. The treated lesions in GAMMA-2 were more heavily calcified, whereby 45% of patients required rotablation in contrast to 26% of patients in GAMMA-1. Despite the differences in lesions, the results between GAMMA-1 and –2 were remarkably similar. Both studies had similar and infrequent in-hospital adverse clinical events (2%). GAMMA-2 patients had a lower post-procedural MLD; perhaps due to increased lesion complexity and the fact that fewer stents were placed in GAMMA-2 patients as compared to GAMMA-1. Similar to GAMMA-1, there was a 52% in-stent and a 40% in-lesion reduction in restenosis frequency. TLR was reduced by 48% and MACE was reduced by 36%. The late thrombosis rate was 4% at 270 days with only 8 weeks of antiplatelet therapy.

BETA Radiation Trials. The beta radiation trials used various types of sources: Y-90, Sr/Y90, and ^{32}P.

BETA WRIST. BETA WRIST examined the efficacy of beta radiation for prevention to ISR, with similar design to the original WRIST study 15. This registry included 50 patients who were treated for ISR in native coronaries 2.5-4.0 mm in diameter with lesions < 50 mm in length. Beta radiation using a 90Y and an afterloader system. Clinical outcomes were compared between these patients and those of the original WRIST cohort (randomized to either placebo or ^{192}Ir). Angiographic restenosis at 6 months in BETA WRIST was 22% with a late total occlusion rate of 12%. In comparison to the historical control group of WRIST, Beta WRIST patients demonstrated a 58% reduction in the rate of target lesion revascularization (TLR) and 53% reduction in TVR at 6 months (p < 0.001). No differences were detected in comparison to the gamma-radiated patients of WRIST. The clinical benefit was maintained at 2-year

follow-up with beta radiation reducing TLR (42% vs. 66%; $p = 0.016$), TVR (46% vs. 72%; $p = 0.009$), and major adverse cardiac events (MACE) (46% vs. 72%; $p = 0/008$) compared to placebo. The efficacy of beta and gamma emitters for the treatment of ISR appeared similar at longer-term follow-up.

START and START 40/20. A pivotal multicenter randomized trial, START (Stents And Radiation Therapy), involved 476 patients in over 55 centers throughout U.S. and Europe, and was designed to determine the efficacy and safety of the Beta-Cath system for the treatment of ISR.[16] Patients were randomized to either placebo or an active radiation train 30 mm in length. The inclusion criteria were single ISR lesions > 50% (by visual assessment) in native coronary target vessels between 2.7 and 4.0 mm in diameter. The target lesion (≤ 20 mm) required treatment with a 20 mm balloon and a 30 mm Source Train. In the radiated patients, the mean lesion length was 16.3 mm in arteries and 2.8 mm in diameter. After successful angioplasty, these patients were treated with the Beta-Cath system containing ^{90}Sr/Y seeds, delivering beta radiation through a closed-end lumen catheter. The dose prescribed at a point 2 mm from center of source axis was based on visual assessment of reference vessel diameter (RVD); 18.4 Gy in RVD ≥ 2.7-£ 3.3 mm and 23 Gy in RVD > 3.3-£ 4.0 mm. The duration of antiplatelet therapy was initially based on operator preference and was modified in early 1999 to at least 90 days of clopidogrel 75 mg/QD following recommendations from the Beta-Cath Trial Data Safety Monitoring Board, where late thrombosis as a complication of brachytherapy was recognized.

At eight months, angiographic restenosis rates in the irradiated segments were 24% vs. 46% in the placebo group ($p < 0.001$). In the irradiated group, TLR was 13% as compared to 22% in control ($p = 0.008$), with similar reductions of TVR (16% vs. 24%; $p = 0.028$), and MACE (18% vs. 26%; $p = 0.026$). There were late thrombotic events in radiated patients.

During multiple studies of radiation, including START, the medical community became aware of the mismatch between the interventional injury length and radiation length, the so-called “geographical miss” phenomenon, with the potential to compromise clinical outcome. The START 40/20 trial was a 207-patient registry that mirrored START, and ensured an adequate irradiation margin with 10 mm of radiation therapy applied proximal and distal to the injury zone (additional 5 mm on each end) (Figure 2). In comparison to the START population, START 40/20 patients were older, had more unstable angina and more prior treatments for ISR, with similar angiographic indices including RVD and lesion length.

Compared to the control arm of START, patients in START 40/20 had; a 44% reduction in restenosis in the analysis segment compared to 36% in radiated arm of START; a 50% reduction in TLR ($p = 0.002$) compared to 42% in radiated arm of START; a 34% reduction in TVR ($p = 0.03$) compared to 34% in START and a 26% reduction in MACE ($p = 0.10$) compared to 31% in the irradiated arm of START. While the START 40/20 registry showed no deleterious effects of adding 10 mm of length to the source train, there was a lack of a relationship between “geographic miss” and clinical or angiographic outcomes for ISR.

INHIBIT and INHIBIT GALILEO. The INHIBIT (Intimal Hyperplasia Inhibition with Beta In-stent Trial), a multicenter randomized study involving 332 patients in 29 U.S. and international sites, examined the efficacy of the GALILEO system for the treatment of IRS.[16,17] The GALILEO system uses a ^{32}P source delivered in a centered delivery catheter with a dose of 20 Gy at a depth of 1 mm into the vessel wall. Potential advantages include homogenous dose distribution, reduced radiation exposure and a perfusion balloon to ensure distal vessel flow was maintained. The study mandated at least 3 months of antiplatelet therapy and 307 patients completed at 9-month clinical follow-up. Radiation was delivered successfully in 315 of the patients, tolerated well in all but 2 patients and there were no adverse effects related to the radiation procedure. At 9 months, treatment with ^{32}P reduced the primary angiographic endpoint of binary restenosis by 67% ($p = 0.0001$) in the stented segment and by 50% ($p = 0.003$) in the analysis segment. There were no differences in the edge effect rates between the active and the control treated groups. The radiated patients had reduced late loss (0.4 vs. 0.6 mm; $p < 0.001$) and improved MLD (1.52 vs. 1.38 mm; $p = 0.01$). At 9 months, ^{32}P significantly reduced rates of TLR (11% vs. 29%; p ¸0.001) and MACE (14% vs. 31%; $p < 0.001$). Tandem positioning to cover diffuse lesions > 22 mm with ^{32}P was safe and effective.

Inhibit Galileo was a registry of 125 patients with same inclusion exclusion criteria of the INHIBIT system. The system was modified to use longer balloons and automatic stepping to address longer lesions and wider margins. The treated group was compared to the control group from INHIBIT and demonstrated similar angiographic and clinical results to the active group from the INHIBIT study (Figure 1).

Other interesting observations were reported from the feasibility studies of the Radiance system using ^{32}P source on a balloon platform. The preliminary results demonstrated safety and efficacy in *de novo* and in-stent restenosis of vein grafts in the SVG BRITE study and for in-stent restenosis in native coronary arteries.

Lessons Learned From Intracoronary Radiation Therapy

Late thrombosis. The phenomenon of late thrombosis following radiation therapy relates to a number of potential triggers including delayed reendothelialization after injury, unhealed dissection, inadequate antiplatelet therapy and use of additional stents.[18] While late thrombosis was first identified in Beta-Cath trial, therapeutic preventive strategies have been driven by data obtained from gamma radiation studies.[19,20] Analysis of WRIST Plus, six months of clopidogrel, and subsequently WRIST 12, twelve months of clopidogrel, demonstrated the benefits of prolonged antiplatelet therapy post vascular brachytherapy. Twelve months of clopidogrel is superior to 6 months in reducing overall major cardiac events (21% vs 36%; $p = 0.01$) and revascularization rates (20% vs 35%; $p = 0.009$) at 15 months for patients with ISR treated with gamma radiation. At least 12 months of clopidogrel therapy should be recommended for patients undergoing radiation therapy for ISR. The Scripps III study confirmed these observations with a 0.2% late thrombosis rate using antiplatelet therapy between 6-12 months following VBT.

The use of eptifibatide as adjunct therapy for patients with ISR that are treated with IRT was examined in the Integrilin WRIST study. Preliminary results showed that

glycoprotein IIb/IIIa inhibitor does not impact the clinical outcome of patients undergoing vascular brachytherapy for in-stent restenosis at 30 days.

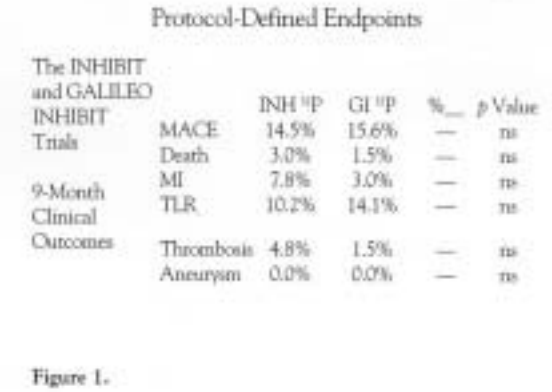

Figure 1.

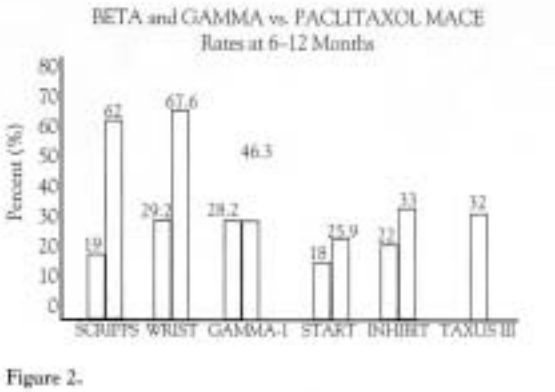

Figure 2.

Edge effect. The development of new stenotic lesions at the proximal and distal edge of the irradiated segment (edge effect) has been a major limitation of vascular brachytherapy and continues to remain unresolved.[21] Edge effect has been seen in both catheter-based and radioactive stent platforms and may relate to either vessel injury (injured but not radiated, i.e., "geographic miss"), or low-dose radiation at the edges of the treatment zone inducing neointimal formation. In the irradiated group of WRIST edge restenosis was observed in 21% of edges with geographic miss and in 4% of edges without geographic miss.[22] Edge recurrence after ^{192}Ir treatment of ISR was the result of neointimal hyperplasia (treatment failure) and lack of positive remodeling after radiation.[23] Recent reports demonstrated that longer source trains to cover the entire injured segment reduce edge effect. Retrospective analyses of various clinical trials utilizing beta sources recommended at least a 10 mm safety margin of radiation from the injured segment is required to minimize the edge effect phenomenon. Pre-clinical experimental work demonstrated that 15 mm coverage will be required to eliminate the edge effect with Ir-192 source.

Long-term safety. Limited data is available pertaining to the long-term safety of intracoronary radiation. Five-year data from both the SCRIPPS and the WRIST studies and two-year follow-up of the Beta WRIST and the START cohorts continue to demonstrate superiority of radiation over control without complications, which could be attributed to the radiation treatment. Long-term studies demonstrate late catch-up, which is responding well to conventional treatment or repeat radiation. It is possible that a higher dose at the index procedure may attenuate this phenomenon and extend the durability of the radiation effect.[8,9]

With the implementation of the lessons learned from the VBT trials, a recent registry of 3,695 patients who underwent commercial use of VBT using the Beta-Cath system in 20 centers, the target vessel revascularization rate at 6 months was 3.8% at 6 months. These results indicate that the real world use of VBT is doing better than the clinical trials and that the technology was optimized and transferred from trials to commercialization.

Vascular brachytherapy versus drug-eluting stents for in-stent restenosis. The initial attempts at using drug-eluting stents for in-stent restenosis have mixed results. Taxus III, using Paclitaxol for the treatment of in-stent restenosis for relatively simple lesions, was associated with overall MACE > 25% at 6 months. The results of the Sirolimus-coated stent for in-stent restenosis are limited to a few patients with mixed results. Few anecdotal reports for the use of drug-eluting stents on patients who failed vascular brachytherapy reported total occlusion and death at 6 months follow-up. Even if the results with the use of drug-eluting stents will be equivocal to vascular brachytherapy, drug-eluting stents will be inferior to VBT from the cost-effectiveness perspective. Also, longer lesions and lesions in the SFA may require longer stents with high levels of drug, which may increase the toxicity to the vessel. Finally, with the latest reports of restenosis that occurs with drug-eluting stents, it appears that VBT will continue to have an important role in the era of drug-eluting stents (Figure 2).

Conclusion. The clinical trials of intracoronary radiation with gamma and beta radiation therapy have demonstrated a dramatic reduction in clinical and angiographic restenosis in patients with in-stent restenosis. The results from the clinical trials have established intracoronary radiation as the therapy of choice for patients with in-stent restenosis, despite potential long-term risks such as malignancy, mandate continued judicious follow-up of all irradiated patients. While the advent of drug-coated stents has been a major advance in interventional cardiology, they have not eliminated restenosis; and in diabetic and small vessels they are associated with nearly 18% restenosis. In addition, their application for in-stent restenosis is unknown at this time, and results of ongoing studies are awaited with anticipation. At present, it is clear that intracoronary radiation therapy remains the cornerstone therapy for in-stent restenosis and will be needed as long as restenosis exists.

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