

Drug-Eluting Stents in Coronary Interventions

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Percutaneous coronary intervention is the main method of non-surgical coronary revascularization, accounting for more than 1,500,000 procedures worldwide every year.¹ Despite technical advancements during recent years, with coronary stenting being the most important, restenosis remains the major problem that hampers the procedure's efficacy. Stent restenosis rates are reported to be 15-20% in ideal lesions, but may occur in over 30-60% of patients with diabetes or with complex lesions (small vessel, long or bifurcation lesions).²⁻⁴ The introduction of drug-eluting stents represents the third revolution in interventional cardiology following balloon angioplasty and stent implantation. Today, we see the appearance of stents coated with anti-restenotic drugs capable of modulating smooth muscle cell proliferation and limiting the restenotic process. This article will summarize this new technology of drug-eluting stents, and describe the results of clinical trials in this field.

Mechanisms of restenosis

Restenosis is the reduction of the lumen size after intravascular interventional procedure. Several cellular and molecular mechanisms occur after balloon inflation.^{5,6} The first mechanism of restenosis is "elastic recoil", the second is "chronic remodelling" and the third is neointimal hyperplasia. The initial response of the elastic fibres of the vascular wall to overstretching by balloon catheter is elastic recoil, responsible for the loss of gain, which cha-

racterizes the early stages of restenosis. The endothelial damage and the exposure of subintimal components cause platelet adherence and aggregation, fibrinogen binding, and thrombus formation. Activated platelets release several mitogens and chemotactic factors, which stimulate smooth-muscle-cell migration and proliferation into the injury site. Finally, a gradual dynamic process that leads to a change in vessel size without an overall change in tissue volume, contributes to the loss of lumen at late times (chronic remodelling). Stenting reduces elastic recoil, but also stimulates neointimal hyperplasia yielding to in-stent restenosis.

To address this problem, we have to understand how smooth muscle cells proliferate. Cell division involves a sequence of tightly programmed steps that are called the cell cycle. The cell cycle is characterized by four active phases. Non-proliferating cells are in a resting state called G₀-phase. When stimulated by growth factors, cells enter the first phase of the cell cycle called G₁-phase. In G₁-phase, cells appear to be resting, but in fact a series of biochemical events are occurring in the cytoplasm to prepare for DNA replication. Cells then progress to S-phase where DNA synthesis occurs, followed by the G₂-phase. In the G₂-phase microtubules assemble to facilitate the process of cell division by aligning chromosomes within the cell nucleus. Finally cells enter the M-phase where mitosis occurs and cells actively separate into two daughter cells, each containing an identical copy of DNA from the parent cell.

Prevention of restenosis

A great deal of effort has been devoted to developing mechanical devices and drugs to prevent restenosis, but none have been proven to be effective.⁷⁻⁹ The introduction of intracoronary radiation has emerged as a promising modality to attenuate the restenotic process, but this technique is only effective in reducing in-stent restenosis.^{10,11} The concept of using immunosuppressive agents for the prevention of the restenosis arises from parallels between tumour cell growth and the benign tissue proliferation which characterizes intimal hyperplasia. Drug-release from the stent surface at the site of vascular injury is an attractive therapeutic method to achieve an effective local concentration of drug for a designed period. The drug can be simply linked to the stent surface, embedded and released from within polymer materials, or surrounded by and released through a carrier. Four key elements that must be considered when developing a drug-eluting stent include the drug, the polymer, the release kinetics and the stent delivery system.¹²

Several immunosuppressive agents are under investigation for their safety and efficacy in the treatment of coronary artery disease. Sirolimus, also known as rapamycin, is a naturally occurring antibiotic compound and has been approved by the FDA for use as an immunosuppressive agent for the prevention of acute renal allograft rejection. Sirolimus has been demonstrated to inhibit smooth muscle cell proliferation and migration in vitro and to reduce neointima formation in animal models of vascular injury.¹³ This drug binds the cytosolic receptor FKBP12 and, unlike other FKBP12 blockers, inhibits an enzyme, known as TOR (target of rapamycin), upregulating p27 levels and inhibiting the phosphorylation of retinoblastoma protein with blockage of the cell cycle progression at the G1-S transition.¹⁴ Once the stent is deployed, sirolimus, delivered by means of a controlled-release polymer matrix that is bound to the stent struts, elutes from the stent and diffuses slowly into the vessel wall over a period of several weeks.

Paclitaxel, first isolated from the bark of the Pacific yew tree *Taxus brevifolia*, is another drug being investigated as an anti-restenotic agent. Paclitaxel has a unique mechanism of action that promotes the assembly of tubulin into stable microtubules that are not able to function properly.¹⁵ Microtubules play an important role in cellular division, cell migration, intracellular signalling, and extracellular secretory

processes. This drug can affect the cell cycle in different areas depending on concentration. While it has predominantly been characterized to affect the cell cycle in the M phase via its pronounced affect on microtubules (cytotoxic effect), more recent data suggest that in low concentrations it stops the cell cycle at the G0/G1 phase (cytostatic effect). The polymer on which the drug has been impregnated is biocompatible and does not elicit any inflammatory response.

Clinical Experience

Designed to assess the feasibility and safety of two different formulations of the sirolimus-eluting stent (CYPHER™) the FIM (First in Man) study involved 45 patients from 2 centres. The fast release formulation releases 100% of the drug in the first 15 days, while the slow release formulation liberates only 15% of the drug in the first 15 days. At one year the minimal lumen diameter (MLD) in lesion for the fast formulation decreased from 2.74 mm following the procedure to 2.32 mm at one year follow-up; for the slow release formulation the MLD of 2.77 mm post-procedure decreased to 2.47 mm at one year.¹⁶ Apart from one patient who sustained a myocardial infarction due to plaque rupture proximal to the stent and another who underwent bypass surgery for ostial left circumflex coronary artery lesion progression, there were no other adverse cardiac events.¹⁷

These results have been confirmed in a large multicenter study (RAVEL), conducted in Europe and in Latin America.¹⁸ In this trial 118 patients randomised to receive a bare metal stent (BX Velocity™) were compared to 120 patients randomised to receive a sirolimus-eluting stent (CYPHER™). Patients with complex coronary lesions were excluded. At 6 months the angiographic restenosis rate was 0% in the CYPHER stent, compared to 26.6% in the bare stent and at 12 months the event free survival was 94% and 71% respectively. At two years' follow-up in a subgroup of patients the beneficial impact of neointimal growth inhibition was persistent.¹⁹ The SIRIUS US trial, a study that randomised 1,058 patients to treatment with sirolimus-coated or bare metal stent, is investigating long-term safety in high-risk lesions for restenosis (2.5-3.5 mm in diameter and 15-30 mm in length).²⁰ The in-stent angiographic restenosis rate at 8 months was 3.2% for the sirolimus and 35.4% for the bare stent and the in-seg-

ment (either within the margins of the stent or 5 mm proximal or distal to the stent) restenosis rates were 8.9% and 36.3% respectively. These favourable results were observed even in diabetic patients, long lesions, proximal left anterior descending coronary artery location and small vessels. Two other multicentre trials recently presented, the E-SIRIUS (involving 350 patients across 35 European sites) and the C-SIRIUS (involving 100 patients from Canada) confirmed the favourable results of the sirolimus-eluting stent in reducing restenosis.^{21,22}

Similar and very promising results were reported using the paclitaxel-eluting stent for coronary lesions in the TAXUS I and II trials. TAXUS I was a prospective, double blind feasibility study randomising 61 patients to receive a TAXUS (n=31) versus control (n=30) stent.²³ Six-month angiographic restenosis rates were 0% for TAXUS versus 10% for control patients (p:NS). At 12 months the major adverse cardiac event rate was 3% in the TAXUS group and 10% in the control group (p:NS). TAXUS II is an efficacy study rather a safety study.²⁴ The study included 536 patients from 19 countries. The patients were randomised to paclitaxel-eluting stent versus bare metal with two different taxol release kinetics (slow and moderate release). In the moderate release formulation most of the drug is released to the tissue within the first 2 days after stent implantation, while the slow release provides continuous drug liberation throughout the first 15-20 days. The angiographic restenosis rate at 6 months in the slow release formulation was 17.9% for the bare and 2.3% for the paclitaxel stent and in the moderate release 20.2% and 4.7% respectively. At 12 months' clinical follow-up the event free survival was 21.7% in the bare metal and 10% in both paclitaxel-eluting stent formulations. Very recently the results of the TAXUS IV trial were reported.²⁵ This is a prospective, double blind, multicentre trial randomising 1,314 patients to receive a slow formulation TAXUS (n=662) versus control (n=652) stent in de novo 10 to 28 mm length lesions in coronary arteries with 2.5 to 3.75 mm diameter. The incidence of target vessel revascularisation, the primary endpoint in this trial, was 3% in the TAXUS and 11.3% in the bare stent group (p<0.0001) and the in-segment angiographic restenosis rates were 7.9% and 26.6% respectively (p<0.0001). More importantly, in diabetic patients the in-segment restenosis rate was 6.4% in the TAXUS and 34.5% in the control group (p<0.0001). Table 1 summarises the findings of the most important multicenter trials with drug-eluting stents.

We conducted a prOspective in Native coronary Artery Stenosis treated with Sirolimus-eluting Stent (ONASSIS) registry including 530 consecutive patients (73% of those treated with percutaneous coronary intervention during a 14 month period). These patients were compared with a control group composed of 398 patients treated with bare stent during a similar time period before the use of drug-eluting stent. Compared with controls, patients treated with the sirolimus-eluting stent had a higher incidence of hypertension (63% vs. 41%, p<0.001) and diabetes mellitus (30% vs. 18%, p<0.001). Multivessel disease was present in 64% in the sirolimus and 49% in the bare stent patients (p<0.001). Clinical presentation of coronary artery disease, history of myocardial infarction or bypass surgery, vessel location and ejection fraction did not differ between the two groups of patients. However, a higher lesion length and number of lesions treated/patient were recorded in the sirolimus-eluting stent group. The clinical success rate (angiographic success without death, Q-wave myocardial infarction, emergency bypass surgery) did not differ between the two groups. Clinical follow-up was obtained in 99% in the sirolimus and 100% in the bare stent group of patients for a mean time of 11.22 ± 3.4 months (range 5-20 months). No difference in death was observed (1.1% in the sirolimus, 1.3% in the bare stent) and myocardial infarction occurred in 0.8% and 1.8% respectively; however, a revascularisation procedure

Table 1. Comparison of the results in the recent multicentre trials using drug-eluting stents. C-SIRIUS and E-SIRIUS were combined and called "New SIRIUS"

	US-SIRIUS (n=1058)	New SIRIUS (n=452)	TAXUS IV (n=1314)
Vessel size (mm)	2.5-3.5	2.5-3.0	2.5-3.75
RVD (mm)	2.8	2.57	2.75
Lesion length (mm)	14.4	14.7	13.4
Stent/Lesion Ratio	1.6	1.7	1.9
Diabetes (%)	26.4	23.3	24.2
Time of follow-up angiography	8 months	8 months	9 months
TLR (%)	16.6 vs. 3.9	20.3 vs. 4.0	11.3 vs. 3.0
Restenosis rate (%) (in segment)	8.9	5.1	7.9
Restenosis rate (%) in diabetics	17.6	10.8	6.4

RVD: reference vessel diameter, TLR: target lesion revascularisation (eluting versus non-eluting).

(either with coronary bypass surgery or repeat percutaneous intervention) was required in 2.1% of patients treated with a sirolimus-eluting stent, compared to 10.1% in the bare stent group ($p < 0.001$). The event free survival (from death, myocardial infarction or revascularisation) was 93.13% in the sirolimus-eluting stent and 83.63% in the bare metal stent ($p = 0.01$).

Drug-eluting stents represent a breakthrough technology for the care of patients with coronary artery disease. Results from multicentre trials suggest that these devices reduce ischaemic target vessel revascularisation rates to $< 10\%$ in most lesion subtypes, which is more than competitive with coronary artery bypass grafting. Ongoing multicentre trials will elucidate the role of drug-eluting stents in multi-vessel disease (ARTS II), patients with diabetes mellitus (FREEDOM), and small vessels (SVELTE). However, cost-effectiveness and long-term reliability remain to be defined.

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