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Hotline Editorial

A new era in the treatment of coronary disease?

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Introduction

The technique of coronary stenting introduced in the early 1990s contributed widely to the enhancement of percutaneous interventions' outcomes in patients with coronary artery disease.

However, the phenomenon of in-stent restenosis has long been the stumbling block of interventional cardiology and the target of many research projects in this field including the use of various devices or radiation therapy, and systemic or local delivery of biochemical substances and drugs.

Indeed, angiographic restenosis, defined as a stenosis or narrowing of the vessel diameter by $\geq 50\%$ at follow-up evaluation (binary restenosis), is still reported in 17–30% of patients following cardiac stenting with uncoated or bare stents.^{1,2} Restenosis following stenting is largely due to neointimal hyperplasia, which is the healing response to the vascular injury induced by stent implantation and mechanical dilatation and translates into proliferation of smooth muscle cells.^{3–6} It is in this context that the technology of site-specific, stent-based drug delivery to inhibit the restenosis process has emerged.

The ability of a wide variety of pharmaceuticals to inhibit restenosis following coronary interventions has been assessed. Evaluation of some of these agents, (actinomycin D, Batismastat and QP2) was discontinued in view of the poor results obtained in the preliminary phases of clinical trials. Among the various drugs investigated, Sirolimus and Paclitaxel stood out as yielding very promising results. So far, however, the longest follow-up study available in the largest group of patients has been conducted with Sirolimus.

Indeed, the local delivery of Sirolimus (rapamycin), a natural macrocyclic lactone which inhibits cytokine and growth factor-mediated cell proliferation in lymphocytes and smooth muscle cells, was shown to reduce neointimal proliferation in animal models as well as in a small, uncontrolled series of patients with coronary artery disease: the First-in-Man pilot study.⁷ A total of 45 patients were included in this non-randomized trial conducted in Sao Paulo, Brazil, and Rotterdam, The Netherlands. Patient outcome was analysed at 4, 6 and 18 months and at 2 years. The 2-year results of the First-in-Man pilot study presented by Dr E. Sousa at the 2002 ACC⁸ showed 'practically no change' when compared with the 1-year findings. Late loss in the slow-release group was -0.09 mm at 2 years, compared to 0.32 mm in the fast-release group. In most patients, neointimal hyperplasia continued to be minimal and lumen was well preserved up to 2 years.

The performance of the Sirolimus-eluting stents compared with that of standard uncoated stents was assessed in the RAVEL study, a randomized, double-blind trial conducted from August 2000 to August 2001 in 19 centres worldwide.⁹ Two hundred and thirty-eight patients with single de novo lesions were randomly assigned to receive a single Sirolimus-coated stent or the bare metal Bx Velocity stent in this double-blind trial. Eligibility criteria included documented stable or unstable angina or silent ischaemia and the presence of a single de novo lesion in a native coronary artery measuring between 2.5 and 3.5 mm.

Patient follow-up was analysed at 1, 6 and 12 months with regard to recurrent stable or unstable angina, major cardiac events and repeat revascularization of the vessel initially treated, the primary endpoint of the trial being angiographic in-stent late loss at 6 months.

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The baseline characteristics of the study patients were comparable in both groups. Patient mean age was 60.7 and 76% were male. Fifty percent of the patients received a stent due to unstable angina. Target vessel was the left anterior descending artery in 50% of patients, right coronary artery in 27% and circumflex in 23%. All target lesions were de novo, though 17.1 and 18.1% of the patients had undergone prior bypass surgery and percutaneous intervention, respectively, due to the presence of other lesions. Ten percent of the patients in the Sirolimus group and 9.5% in the uncoated stent group received GPIIb/IIIa inhibitors.

Stent deployment was successfully performed in 96% of patients in the Sirolimus group and in 93.1% in the uncoated group (NS).

Angiographic follow-up obtained in 88.7% of the study patients showed that the mean in-stent minimum luminal diameter was notably larger in the group of patients randomly assigned to implantation of a Sirolimus stent. Mean in-stent late loss, percent diameter stenosis and binary restenosis rates were -0.01 mm, 14.7 and 0%, respectively, in the Sirolimus group versus 0.80 mm, 36.5 and 26.2%, respectively, in the uncoated stent group.

An intra-vascular ultrasound analysis conducted at 6 months in a subset of patients showed no difference between the two groups in-stent, total vessel and plaque behind the stent volume.

However, neointimal hyperplasia (2 ± 5 versus 37 ± 28 mm³) and percent volume obstruction (1 ± 3 versus $29 \pm 20\%$) were markedly smaller in the Sirolimus group compared with the bare stent group and no edge effect, aneurysm formation, intra-stent thrombosis or persistent dissection were observed.

Overall, the rate of major adverse cardiac events was 5.8% in the Sirolimus group versus 28.8% in the uncoated stent group. The Sirolimus coating of the active stent was not associated with any untoward effect. The 0% restenosis rate observed at 6-month follow-up in the Sirolimus-eluting stent group compared to 26% in the uncoated stent group, and the 94% event-free survival rate at 1 year raised high hopes in the interventional cardiology community.

The US Pivotal Trial, SIRIUS, was initiated in order to evaluate further the efficiency of Sirolimus stents. SIRIUS is a large-scale, randomized, double-blind, controlled clinical trial involving 53 US treatment centres and 1101 patients investigating CYPHER™ Sirolimus-eluting stent. Eight-month angiographic follow-up presented in Washington in September 2002 showed virtually no in-stent late lumen loss (0.17 mm) in patients treated with the CYPHER™ Sirolimus-eluting stent, mirroring the

6-month findings of the RAVEL study and the 2-year findings of the First-in-Man study. The 3.2% rate of angiographic in-stent restenosis – representing a 91% reduction versus the control arm (bare metal stent) – supports the findings of earlier studies. At 9-month follow-up, the event-free survival rate was 92.7% in the Sirolimus-treated cohort versus 80.7% in the control group. As in the RAVEL study, there was no case of acute, sub-acute or late thrombosis in the Sirolimus-eluting stent arm of the study, despite only 3 months of anti-platelet therapy and the placement of overlapping stents in a significant number of patients (27%).

In order to test the hypothesis that Sirolimus-eluting stents might also be efficient in the treatment of in-stent restenosis investigators from Sao Paulo, Brazil, and Rotterdam, The Netherlands, conducted a feasibility study (ISR) in a group of 41 patients. The earlier 4-month follow-up data had shown minimally low in-stent late lumen loss, zero restenosis, no TLR, stent thrombus or death in Sao Paulo. However, more events were reported in the Rotterdam cohort involving very complex patients (transplanted patients already treated by radiation therapy and multiple stenting).

It is also important to underline that, though unable to replicate the 0% restenosis rate reported in RAVEL, results from other trials (TAXUS, ELUTES, ASPECT) using taxol-derived agents have shown favourable 6-month angiographic binary restenosis rates compared to uncoated stents.

Are drug-eluting stents cost-effective?

Though drug-eluting stents are viewed as a revolutionary tool in the management of coronary artery disease, their cost (three times that of bare stents) is a major concern and has been the subject of many discussions.

The cost analysis performed by Van Hout et al. in The Netherlands on the basis of the RAVEL trial tends to show that the higher initial cost of the Sirolimus-eluting stents compared to standard uncoated stents is counterbalanced by the absence of repeat intervention at 1-year follow-up. In this Dutch study, total direct medical costs were Euros 9969 in the Sirolimus group versus Euros 9915 in the uncoated stent group.

For the time being, given the cost containment policy in most countries, there is a strong probability that treatment with drug-eluting stents will unfortunately be limited to patients at high risk for restenosis, diabetics and patients with lesions in small vessels.

Nevertheless, one can expect that, as with most new technologies, the price of these new devices will decrease as they become increasingly used, thus enabling the operators to include them in their routine arsenal.

The clinical implications

When assessing any new technology the busy interventional cardiologist will ask: Is it safe? Is it effective? In which patients can I use it? Can I use overlapping stents?

In the case of the Sirolimus-eluting stent, available pre-clinical and clinical trial data confirm that it is safe (at least up to 2 years), that it is effective in de novo lesions and suitable for use in a wide range of patients. Data from the SIRIUS trial appear to support its use in overlapping stents.

The use of drug-eluting stents is unlikely to reduce the already low rates of in-hospital death and myocardial infarction in the general patient population already treated by percutaneous coronary intervention (PCI). The major impact of drug-eluting stents is likely to be among high-risk sub-groups and patients with lesions currently not considered amenable to PCI such as left main lesions or triple vessel disease. However, a reduction in late mortality may be expected in diabetic patients.

Diabetic patients represent a seriously high-risk group, especially in the occlusive form of the disease, which is a powerful predictor of long-term (10-year) mortality in diabetic patients after coronary balloon angioplasty.¹⁰ Findings from the Bypass Angioplasty Revascularization Investigation (BARI) also support the concept that maintaining coronary artery patency is critical to longer-term outcomes in patients with diabetes.

We are also likely to see a very substantial reduction in repeat revascularization, from an average of 14% for trials with conventional stents to 4% for drug-eluting stent trials overall.

Moreover, it seems likely that the use of drug-eluting stents will be extended to patients cur-

rently not eligible for PTCA due to unfavourable anatomic presentations; this could lead to a dramatic reduction in the rate of CABG surgery which might become a last resort treatment strategy.

However, only when the 18 on-going or planned investigational studies evaluating the Sirolimus-eluting stent across a range of challenging lesion types (bifurcation, left main, chronic total occlusion and acute MI) and patient groups (diabetics and CABG) as well as the numerous series of trials with other drugs report their findings, will the interventional cardiology community know which patients are most likely to benefit from this promising and innovative technology.

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