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European Heart Journal (2001) **22**, 2054–2057

doi:10.1053/euhj.2001.2950, available online at <http://www.idealibrary.com> on IDEAL®

The sirolimus coated stent: will the Achilles heel of interventional cardiology finally be cured?

See page 2125, doi:10.1053/euhj.2001.2892 for the article to which this Editorial refers

Restenosis has been identified as the Achilles heel of percutaneous revascularization. Stenting has been established as an effective procedure for reducing acute complications and long-term restenosis, using mechanical scaffolding principles to prevent recoil and negative arterial remodelling and to secure the largest possible lumen at the completion of the procedure. However, long-term success is still limited by in-stent restenosis due to neointimal proliferation in response to the arterial injury.

The search for effective prevention of in-stent restenosis started in the early days of stenting. Mechanical techniques such as atherectomy prior to stenting, optimal methods to monitor stent expansion etc. led to only limited success. Intracoronary radiation has been established as an effective method to prevent restenosis^[1], yet it is limited by potential long-term sequella such as edge restenosis and late thrombosis^[2] and its very long follow-up effects are unknown. In addition, the combined use of radiation and stenting in de-novo and restenotic lesions maybe associated with an increased risk of late thrombosis. Numerous pharmacological approaches to reduce restenosis

have failed, possibly due to insufficient local drug concentrations, inadequate kinetics and other factors.

Local drug release at the site of vascular injury via a polymeric-coated stent is an elegant approach to achieve effective local concentration for a planned duration^[3]. However, the safety and efficiency of such an approach critically depends on the delicate combination of the drug, the polymer and the kinetics of the release. Among multiple possible effective compounds, a number of stents coated with antiproliferative drugs are currently being investigated to assess their efficiency and safety in the prevention of restenosis. Among the agents studied in different stent models, those with the largest animal and clinical experience are paclitaxel, actinomycin D and sirolimus.

Sirolimus (rapamycin, Rapamune®), a macrocyclic lactone antibiotic produced by *Streptomyces hygroscopicus*, was originally developed as an anticandidal agent in 1975^[4]. It is a unique compound with pharmacological activity targeted at various phases of the cell cycle. It has potent, immunosuppressant, and antitumour properties — inhibiting the translation of key mRNAs of proteins required for cell cycle progression from G1 to S phase. The Food and Drug Administration approved it for the prophylaxis of

Table 1 Intravascular ultrasound measurements from the first 27 Brazilian patients who underwent 1-year follow-up

	Postprocedural	4 months	12 months
Stent volume (mm ³)	125	134	127
Lumen volume (mm ³)	125	134	124
Neointimal hyperplasia volume (mm ³)	0.0	0.4	2.4
% obstruction volume	0	0.3	2.3

renal transplant rejection in 1999^[5]. Sirolimus binds intracellularly to the immunophilin FK506 binding protein 12, and the resultant complex inhibits the activity of a protein kinase termed the mammalian target of rapamycin (mTOR)^[6]. The inhibition of mTOR, in turn, blocks signals to two separate downstream pathways which control the translation of specific mRNAs required for cell cycle traverse from G1 to S phase. Blocking mTOR affects the activity of the 40S ribosomal protein S6 kinase and the function of the eukaryotic initiation factor 4E-binding protein-1, leading to growth arrest in the G1 phase of the cell cycle. In addition, sirolimus increases p27 levels, prevents cyclin-dependent kinase activation, inhibits retinoblastoma protein (pRb) phosphorylation, and accelerates the turnover of cyclin D1 that leads to a deficiency of active cdk4/cyclin D1 complexes, all of which can inhibit cell cycle traverse at the G1/S phase transition^[7].

Sirolimus is cytostatic and not cytotoxic, meaning that it prevents cell replication rather than killing cells. This drug selectively targets proliferating smooth muscle cells. It diffuses across vascular tissue and has a prolonged half-life in tissue. It inhibits the proliferation of both rat and human smooth muscle cells *in vitro*^[8] and reduces intimal thickening in animal models of vascular injury^[9,10]. The sirolimus-coated BX Velocity[™] stent is a third-generation balloon-expandable stent that contains a fixed amount of sirolimus per unit of metal surface area delivered in a mixture of non-negotiable polymer.

In an eminent pilot study, the BX Velocity[™] stent coated with sirolimus has been used in 45 patients for coronary lesions less than 18 mm long and with a reference vessel diameter of 3.0–3.5 mm^[11,12]. The clinical and 6 month angiographic and three-dimensional (3D) IVUS follow-up data for the 15 patients treated in Rotterdam reported in this issue^[13] shows almost no proliferation within the stent. Clinical events at 6-month follow-up were one death from an unrelated cerebrovascular incident, and one sub-acute stent thrombosis attributed to edge dissection. The volumetric 3D IVUS analysis was performed by independent core laboratories on the stented segment

(18 mm) and on two edge segments in a manner similar to that in the ERASER study^[14], which compared treatment with abciximab to placebo, in patients stented with a balloon-expandable stent (Palmaz–Schatz). The similar 3D volumetric analysis method allowed the investigators to compare their current data with equivalent historical controls from the control arm of that study. The stents at 6 month follow-up were well covered with a thin layer of neointimal hyperplasia with no evidence of in-stent or edge restenosis of IVUS. Neointimal, hyperplasia was minimal at 4 months and remained so at 1 year (Table 1), with good lumen preservatin. A dramatic difference in neointima formation compared to the ERASER control arm was noted.

These data are indeed impressive and are of such magnitude that they can theoretically change our approach to coronary interventions. However, with respect to the current stent and other active stent coatings, large well-controlled clinical trials and longer follow-up periods are extremely important to show the magnitude of the effect of the antiproliferative stents in simple lesions as well as in long lesions and small vessels. In addition, large randomized studies should indicate the long-term biocompatibility of the sent-polymer material once the drug concentration wanes.

The following important studies with the sirolimus-coated BX Velocity[™] balloon-expandable coated stent that are currently underway will provide part or all of the answers to these questions.

RAVEL included 220 patients in 21 sites in Europe and the U.S. and compared coated to non-coated stents in single de-novo lesions between 2.5 and 3.5 mm. The 6 month follow-up angiographic results were reported at the last ESC meeting and revealed no restenosis (>50%) in the sirolimus group (Table 2).

SIRIUS is a multicentre, randomized, double-blind study of this stent in the treatment of patients with de novo coronary artery lesions. It is intended to include 1100 patients from 55 centres. Inclusion criteria include single de novo non-thrombotic non-ostial native lesions (15–30 mm long, 2.5–3.5 mm diameter). Clinical follow up is planned for up to 5 years with

Table 2 RAVEL study — comparison of sirolimus-coated and non-coated stents

Endpoint	Sirolimus group	Control group	P value
Late loss (mm)	-0.01 ± 0.33	0.8 ± 0.53	<0.0001
Restenosis (%)	0	26	<0.0001
No MACE (%)	96.7%	72.9%	<0.0001

8 month angiographic and IVUS follow-up. Primary end-points are in-stent minimal lumen diameter and secondary end-points are MACE (death, MI, emergency surgery or repeat revascularization). The E-SIRIUS will randomize 350 patients (175 patients/study arm) with a similar protocol and end-points, from 35 European centres.

The saga of antiproliferative stents has already started. Sirolimus coating may be the first successful attempt, but many other drugs are currently being evaluated. Each one of the drugs may have its own specific optimal kinetics and side effects. Polymer loading has to be tailored specifically to assure the proper drug release. Toxicity effects may be markedly different between drugs and the therapeutic range of a drug may be critically important even with the specific local releases. Vessel healing with re-endothelialization is an important integral part of this treatment. A drug eluting stent should show a healed stented vessel characterized by endothelialization, absence of fibrin or fibrinoid deposits and lack of excessive inflammation or haemorrhage. The proof of efficiency and safety will probably have to be matched for each drug-polymer combination. The specifics of stent design assuring optimum drug distribution in addition to optimal scaffolding may be an additional parameter in the design considerations for drug elution.

While the initial results are indeed supportive of an extreme antiproliferative effect, while not interfering with strut coverage, concerns need to be addressed in the ongoing clinical trials for any type of drug eluting stent. Potential toxic effects of the drug may lead to excessive necrosis of smooth muscle cells in the vicinity of stent struts, enhancing an inflammatory response. An impaired healing process may lead to an excessive risk of late thrombosis. The active drug may interfere with the arterial wall structure leading to possible weakening and expansion of the arterial wall. The polymer itself may provoke an inflammatory response after the drug has been released from the stent, leading to shifting of restenosis to later time periods than classically seen with metal stents.

The data so far for the sirolimus coated stent do not support any of these concerns. If the results

reported in the pilot evaluation presented here are maintained in the larger studies, and will not be affected by as yet unknown side effects over a longer time frame, the field of interventional cardiology will change its paradigm. Treatment of single or multi-vessel diseases using stents will only be limited by anatomical variables. Long-term efficiency of treatment in cases of acute success will be secured. Treatment of unprotected left main lesions will not be limited by the hazard of possible sudden death due to silent restenosis of the stented stem. The magnitude of the effect may be similar in small vessels, diabetic patients and long lesions. Restenosis may not be eradicated, but the Achilles heel of percutaneous interventions may be cured.

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