Rapamycin eluting stent: the onset of a new era in interventional cardiology

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EDITORIAL

Rapamycin eluting stent: the onset of a new era in interventional cardiology

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Drug eluting stents represent one of the fastest growing fields in interventional cardiology today.

At the congress of the European Society of Cardiology in Amsterdam in 2000, I (PWS) was asked to give the Andreas Gruentzig Lecture. In the week preceding the lecture, we re-angiographied patients 32 and 33 of the initial cohort of patients who had received a rapamycin eluting stent in Sao Paulo and in Rotterdam. Scrutinising the 4–6 month angiographic and ultrasonic results of these patients, I became overwhelmingly convinced that we were the privileged witnesses of a new phenomenon: the almost complete abolition of intra-stent neointimal proliferation. Colleagues, invasive and non-invasive cardiologists, old friends, and financial analysts were surprised by the unusual "excess of enthusiasm" coming from somebody who has built over the years a reputation as a critical assessor, never one to be carried away by the hype of a new wave in interventional cardiology. In the history of this field I have recognised (and "got excited" by, as my American colleagues used to put it) only two revolutionary developments: the introduction of the moveable and steerable guidewire by John Simpson, and the advent of the stent (Palmaz-Schatz, Wallstent). The drug eluting stent is the third such development, and almost one year later I would like to restate the fact that we are entering a new era in interventional cardiology. Why? Because the principle of an eluting stent is sound, and because the three major technical challenges have been mastered—the controlled release of an efficient drug from a stable coating.

THE PRINCIPLE

Drug administration for the prevention of restenosis has been tested in the past—with disappointing results throughout. A proposed explanation for the repeated failure of clinical drug studies has been that agents given systematically cannot reach sufficient concentrations in injured arteries, which has a signficant impact on the restenotic process. Local drug administration offers advantages. The active drug is applied to the vessel at the precise site and at the time of vessel injury. Local drug delivery is able to achieve higher tissue concentrations of the drug. No additional material or procedures are required. Systemic release is minimal and may reduce the risk of remote systemic toxicity.

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THE DELIVERY VEHICLE

The delivery vehicle must fulfil pharmacological, pharmacokinetic, and mechanical requirements. The release of the drug into the vessel must take place in a manner that is consistent with the drug's mode of action. Drug release must be predictable and in a controlled concentration and time. The delivery vehicle must be suitable for sterilisation; it must follow the geometric change of configuration during stent expansion and resist mechanical injury caused by the inflation of the balloon. Today these problems are controlled, guaranteeing intact coating during clinical application.

THE DRUG

The drug should be one that inhibits the multiple components of the complex restenosis process. Uncontrolled neointimal tissue accumulation shows some parallels to tumour growth, thus the use of antitumorous strategies seems to be a logical consequence. Numerous pharmacological agents with antiproliferative properties have been tested for their potential to inhibit restenosis.

Rapamycin (sirolimus) has been approved by the US Food and Drug Administration for the prophylaxis of renal transplant rejection. It is a naturally occurring macrocyclic lactone which is highly effective in preventing the onset and severity of disease in several animal models of autoimmune disease, such as insulin dependent diabetes mellitus, systemic lupus erythematosus, and arthritis.

RAPAMYCIN'S MECHANISM OF ACTION

The class of macrocyclic immunosuppressive agents (rapamycin, cyclosporin A, tacrolimus FK506) bind to specific cytosolic proteins called immunophilins (for example, FK506 binding protein 12) to gain their immunosuppressive activity. Rapamycin blocks G1 to S cell cycle progression by interacting with a specific target protein (mTOR, mammalian target of rapamycin) and inhibits its activation. The inhibition of mTOR suppresses cytokine driven (IL-2, IL-4, IL-7, and IL-15) T cell proliferation. mTOR is a key

Abbreviations: FR, fast release; IL, interleukin; IVUS, intravascular ultrasound; mTOR, mammalian target of rapamycin; PBMA, polybutylmethacrylate; PCNA, proliferating cell nuclear antigen; PEVA, polyethylenevinylacetate; RAVEL, randomised study with sirolimus coated BX Velocity balloon expandable stent in the treatment of patients with de novo native coronary lesions; SR, slow release; VEGF, vascular endothelial growth factor

regulatory kinase and its inhibition has several important effects, including: the inhibition of translation of a family of mRNAs that code for proteins essential for cell cycle progression; the inhibition of IL-2 induced transcription of proliferating cell nuclear antigen (PCNA) that is essential for DNA replication; the blocking of CD28-mediated sustained upregulation of IL-2 transcription in T cells; and the inhibition of the kinase activity of the cdk4/cyclinD and cdk2/cyclinE complexes, essential for cell cycle progression. The mechanism of action is distinct from other immunosuppressive drugs that act solely by inhibiting DNA synthesis, such as mycophenolate mofetil and azathioprine. Rapamycin is synergistic with cyclosporin A and has much lower toxicity than other immunosuppressive agents.

Rapamycin prevents proliferation of T cells but also proliferation[1] and migration of smooth muscle cells. Gregory and colleagues demonstrated that intraperitoneal administration of rapamycin resulted in a dose dependent inhibition of arterial intimal thickening caused by either chronic alloimmune or mechanical injury in a rat model.[2 3] Subsequent studies reported that rapamycin inhibited both human and rat vascular smooth muscle cell proliferation in vitro by blocking G_i/S transition. The inhibition of proliferation was mediated by rapamycin binding to its cytosolic receptor, FK506 binding protein 12, and associated with reduced cdk2 activity and protein retinoblastom phosphorylation.[4 5]

Gallo and colleagues recently showed that systemic rapamycin treatment significantly reduces the proliferative response after coronary angioplasty in the porcine model.[6] The antiproliferative effects of rapamycin after angioplasty were attributed to an inhibition of the pRB phosphorylation preventing the down regulation of $p27^{kip1}$. Thus, the antiproliferative activity of rapamycin after balloon arterial injury in conjunction with its immunosuppressive properties suggests that this drug could also be useful for the prevention of in-stent restenosis.

This hypothesis is further supported by findings in human carotid arteries.[7] A robust upregulation of FK506 binding protein 12 was detected in the neointimal tissue of restenotic lesions, whereas no FK506 binding protein 12 was detectable in smooth muscle cells from control media.

THE RAPAMYCIN ELUTING STENT

The rapamycin coated BX Velocity stent is fabricated from medical 316 LS stainless steel. It is available in a length of 18 mm and in two cell configurations (6 cell configuration: expanded diameter 2.5–3.25 mm) and 7 cell design (expanded diameter 3.5–3.75 mm). The stent contains 140 μg rapamycin/cm^2 which gives a total rapamycin content of 153 μg on the 6 cell stent and 180 μg on the 7 cell stent. The coating formulation consists of 30% rapamycin by weight in a 50:50 mixture of the polymers polyethylenevinylacetate (PEVA) and polybutylmethacrylate (PBMA).

IN VIVO PHARMACOKINETICS

In vivo pharmacokinetics studies in the porcine coronary model demonstrated that the whole blood concentration of rapamycin peaks at 1 hour (mean (SD) 2.63 (0.74) ng/ml) after stent deployment and then declines below the lower limit of detection (0.4 ng/ml) by three days. The total arterial tissue concentration of rapamycin is 97 (13) ng/artery and the residual stent content is 71 (10) μg at three days. The amount of residual rapamycin on the stent at three days is 43% of the initial quantity loaded on the stent. A modification of the coating provides similar arterial tissue concentrations at 28 days. These data document the ability to deliver and achieve a potentially therapeutic arterial tissue concentration of rapamycin in the porcine model and insignificant concentrations in the systemic circulation using the non-erodible methacrylate and ethylene based copolymer matrix.

PRECLINICAL EFFICACY STUDIES

Preclinical efficacy studies demonstrated a 35–50% reduction in in-stent neointimal hyperplasia for the rapamycin coated stents as compared with bare metal stents at 28 days in the porcine and rabbit model.[8] Histological assessment revealed the presence of typical cellular components of the neointima and a similar degree of re-endothelialisation for the rapamycin as compared with the bare metal stents. The morphology of non-stented reference arterial wall sections, including the vessel area, neointimal area, and per cent area stenosis was similar for the metal and each of the drug coated stents. A semiquantitative histological grading system demonstrated less smooth muscle cell colonisation and more residual fibrin deposition for the rapamycin eluting stents as compared with the bare metal stents. Therefore, critical reparative events, such as endothelialisation and smooth muscle cell colonisation of the neointima, with rapamycin eluting stents occur in a similar temporal sequence as observed with bare metal stents. The focal remnants of residual fibrin deposition observed in the vessel with rapamycin coated stents may reflect a delay in arterial repair or impaired fibrin degradation secondary to the local effects of the drug.

CLINICAL DATA

The first clinical application of the rapamycin coated stent was performed in Sao Paulo and Rotterdam. Thirty patients with angina pectoris were electively treated with two different formulations of the rapamycin coated BX Velocity stent (Cordis) (slow release [SR] n = 15, and fast release [FR], n = 15). All stents were successfully delivered, and patients were discharged without clinical complications. At four months' follow up, there was minimal neointimal hyperplasia in both groups as assessed by IVUS and quantitative coronary angiography (in-stent late loss, 0.09 (0.03) mm [SR] and 0.02 (0.3) mm [FR]). No in-stent or edge restenosis was observed. No major clinical events (stent thrombosis, repeat revascularisation, myocardial infarction, death) had occurred by 12 months.[9] At one year follow up, IVUS volumetric analysis and angiography indicated minimal amounts of neointimal hyperplasia that were scarcely different from the four month data in both groups, with some patients showing no evidence of hyperplasia whatsoever. There were no major adverse cardiac events and no restenosis in either of the groups. One late acute myocardial infarction occurred in the FR group at 14 months.[10] In Rotterdam,15 patients were treated, and quantitative angiography and three dimensional quantitative IVUS were performed at implantation and at six months' follow up. All stent implantations were successful; one patient died on day 2 of cerebral haemorrhage and one patient suffered subacute stent occlusion caused by edge dissection. At nine months' follow up no further adverse events had occurred and all patients were angina-free. Quantitative coronary angiography revealed essentially no change in minimal lumen diameter and per cent diameter stenosis by angiographic criteria, and hence no in-lesion or in-stent angiographic restenosis was observed. Quantitative ultrasound showed that intimal hyperplasia volume and per cent obstruction volume at follow up were negligible (5.3 mm^3 and 1.8%, respectively). No edge effect was observed in the segment proximal and distal to the stent.[11]

These first clinical results are spectacular, as they convincingly demonstrate the absence of neointimal proliferation in all patients within the first six months after coronary stent implantation, a phenomenon which has never been reported in the past. If this promise—namely, the elimination of restenosis—becomes reality we will witness the onset of a new era in interventional cardiology and the revolution of catheter based intervention, bypass surgery, and health care economics! These enormous potential implications are the key for

today's enthusiasm. However, more than 20 years of experience in the investigation of restenosis force us to think of a possible Achilles' heel. In fact, a lot of unanswered questions still have to be resolved. First of all, controlled clinical data are needed. Furthermore, long term studies are required to elucidate if the drug is permanently inhibiting neointima growth or simply delaying the formation of neointima. Additionally, the recent experience with vascular brachytherapy alerts us to search for "unexpected" phenomena such as positive remodelling, late stent malapposition, edge effect, or late thrombosis. Again, meticulous long term clinical, angiographic, and IVUS follow up will be mandatory.

ONE YEAR LATER: DOES THE RAVEL STUDY REVEAL THE FULL STORY?

The randomised study RAVEL, using the rapamycin coated BX Velocity balloon expandable stent in the treatment of patients with de novo lesions in native coronary arteries, is a multicentre, prospective, randomised double blind clinical trial comparing a bare metal stent with the drug coated stent. Two hundred and twenty patients were randomised to a single rapamycin coated stent (140 $\mu g/cm^2$) versus a bare metal BX Velocity stent. At six months' follow up, the restenosis rate of the treated group was zero, the loss in minimal lumen diameter was zero, there was no target lesion reintervention, and the event-free survival was 96.5%.[12]

UPCOMING CLINICAL TRIALS

The SIRIUS study is a multicentre, prospective, randomised double blind trial that is being conducted in 55 centres in the USA. Eleven hundred patients with focal de novo native coronary arterial lesions (2.5–3.5 mm diameter, 15–30 mm long) will be randomised to treatment with rapamycin coated or bare metal BX Velocity balloon expandable stents. The primary end points of the SIRIUS trial are target vessel failure (death, myocardial infarction, target lesion revascularisation) at nine months. In addition, secondary end points are core laboratory analysis of angiographic and IVUS data to determine treatment effects on neointimal hyperplasia and in-stent restenosis. Clinical follow up will extend to three years in order to assess for late events. In addition to the pivotal RAVEL and SIRIUS trials, feasibility studies are ongoing to assess efficacy of rapamycin coated stents in more complex lesion subsets such as in-stent restenosis.

Drug eluting stents represent one of the fastest growing fields in interventional cardiology today. The exploitation of different classes of drugs which are potential candidates for the inhibition of restenosis, in combination with novel drug delivery systems or local gene therapy (for example, local expression of proliferation regulatory genes, transfer of cytotoxic genes, vascular endothelial growth factor (VEGF)) will continue. The multicentre trials will help to answer some of the most important clinical questions and determine whether this really reflects the eve of a "new era" or just a "new vogue" in interventional cardiology.

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