Coated stents: a novel approach to prevent in-stent restenosis

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Introduction

Twenty years after the first percutaneous coronary angioplasty performed by Andreas Gruntzig, restenosis – the process of late arterial renarrowing at the site of initially successful intervention – remains the major limitation of this procedure[1]. The dream of an effective treatment for restenosis has eluded decades of effort by an army of investigators. Scores of devices, hundreds of drugs, and innumerable revascularization "strategies" have failed to eliminate the 10 to 50% risk of recurrence after angioplasty[1]. No matter how much skill, experience, time, and effort the interventionist brings to the table, restenosis can entirely reverse a perfect procedural result within months and remains a vexing problem of percutaneous coronary intervention. However, the reasons by which restenosis was unsuccessfully treated might be related to the fact that the complex mechanisms of restenosis were only recently clarified with the use of intravascular ultrasound (IVUS)[1]. A recent study by Mintz et al.[2] using IVUS demonstrated that restenosis appears to be determined primarily by the direction and magnitude of vessel wall remodeling; therefore, a decrease in the external elastic membrane and, in part, the proliferation of smooth muscle cells explain restenosis after balloon angioplasty. Although stent deployment has been shown to reduce the rate of restenosis[1] compared with balloon angioplasty, in-stent restenosis is still a significant and (with increased stent implantation in interventional cardiology) a growing clinical problem. Using IVUS technology, Hoffmann et al.[3] demonstrated that in stented segments, late lumen area correlated strongly with tissue growth but only weakly with remodeling. Therefore, using the IVUS analysis it has been demonstrated that chronic stent recoil is minimal, late lumen loss and in-stent restenosis are due to neointima tissue proliferation. In the clinical setting, the most promising approach to prevent restenosis has been the application of intracoronary radiation; however, some relevant side effects (edge restenosis and late thrombosis) have been reported[4]. Until now, only the efficacy provided by vascular brachytherapy has offered hope to patients with in-stent restenosis[4]. Some investigators have also shown that gene therapy approaches could be used in experimental animal models to reduce neointima formation after balloon injury[1]. However, at the present time cost/benefit analysis and the possibility of plasmid DNA stable integration of in vascular smooth muscle cell genome leading to unwanted biological effects, do not allow the use of a gene therapy approach in the clinical setting to prevent restenosis.

It should be pointed out that numerous pharmacological approaches to reduce restenosis have failed, possibly due to insufficient local drug concentrations. Delivering medication directly to the site of vascular injury via polymeric-coated stents is a rational approach to achieve adequate local drug delivery[5].

Coated stents

Treatment of symptomatic atherosclerotic heart disease has become increasingly focused on percutaneous catheter-based techniques. However, restenosis limits

coronary angioplasty benefit. Recently the use of stent has been introduced to achieve a bigger luminal diameter and to treat vascular dissections. Unfortunately, stent implantation also markedly induces vascular smooth muscle cell proliferation. In fact, neointima formation is the only mechanism responsible for restenosis after stent deployment that occurs in about 20% of Benestent-like lesions and in about 50% of long lesions and vein grafts. Previous studies using IVUS demonstrated that stent deployment abolishes arterial remodeling but triggers and may actually increase vascular smooth muscle cell proliferation responsible for neointima formation. In our laboratory, we have previously shown that local delivery of a transdominant negative H-*ras* gene markedly reduces neointima formation after balloon injury in rats[1]. The inhibition of a protein downstream *ras*, MAPKK, also prevents neointima formation after balloon injury[1].

Several clinical studies demonstrated the beneficial effects of HMG-CoA reductase inhibitors in primary and secondary prevention in reducing cardiovascular mortality[6]. The antiatherosclerotic effect of these drugs has been linked to their hypolipidemic properties[6]. However, clinical studies demonstrated that the potency of these drugs in reducing cardiovascular events is independent of basal cholesterol levels[6]. In fact, the HMG-CoA reductase inhibitors, such as simvastatin, not only reduce plasma cholesterol levels, but also competitively inhibit intracellular synthesis of mevalonate, a precursor of non-sterol compounds such as geranylgeranyl and farnesyl involved in cell functions and proliferation. The effect of simvastatin on farnesyl radical synthesis is responsible for the intracellular inhibition of *ras-raf-MAPKK* protein signal transduction pathway activation. *Ras* proteins are members of a family of GTPases which includes proteins involved in protein synthesis and signal transduction (heterotrimeric G protein). The anchorage of GTPases to various cellular membranes is also critical for their proper function and is regulated by prenyltransferases. These enzymes catalize the reaction which leads to linkage of farnesyl and geranylgeranyl groups to the *ras* protein. In our laboratory, we demonstrated that the inhibition of the *ras* protein by simvastatin administration reduced restenosis after experimental balloon angioplasty[6].

cAMP-PKA signaling activation plays an important role in the regulation of smooth muscle cell proliferation[7]. Therefore, the inhibition of cellular *ras* or the activation of cAMP signaling could be used to prevent neointima formation after vascular injury[7]. However, cAMP pathway stimulation is pharmacologically feasible in clinical setting, and this may represent a clear advantage over the gene therapy approach. In our previous study, the activation of cAMP-PKA signaling was obtained using 8-Br-cAMP local administration mediated by pluronic gel that however is not clinically feasible[7]. In this study, we demonstrated that 8-Cl-cAMP reduces vascular smooth muscle cell proliferation *in vitro* and neointima formation induced by balloon injury after systemic administration *in vivo*. Since it has been shown and well demonstrated that both 8-Cl-cAMP and HMG-CoA inhibitors can be used and are well tolerated in humans, these data might have an important clinical relevance especially in the setting of delivering medication directly to the site of vascular injury via polymeric-coated stents.

Rapamycin is a potent cytostatic agent inhibiting vascular smooth muscle cell migration and proliferation *in vitro* and *in vivo* after balloon angioplasty or stenting in different animal models. Like cyclosporin A and tacrolimus (FK506), sirolimus binds to specific cytosolic proteins. However, the mechanism of action of sirolimus is distinct from other immunosuppressive agents that act solely by inhibiting DNA synthesis. The sirolimus:FKBP complex binds to a specific cell-cycle regulatory protein, the mTOR (mammalian target of rapamycin), and inhibits its activation. The inhibition of mTOR induces cell-cycle arrest in late G1 phase. The up-regulation of FK506-binding protein 12 (FKBP12) observed in human neointima smooth muscle cells additionally supports the potential antirestenotic effect of sirolimus. Preclinical data have demonstrated the efficacy of both systemic and local administration (via drug-eluting stent) of sirolimus in reducing neointima hyperplasia in different models of restenosis. Nevertheless, Sousa et al.[8,9] provide a first glimpse at the 1-year data after the implantation of sirolimus-eluting stents in humans[8] after a previous report on the safety of this novel approach[9]. The report describes a very small, non-controlled registry, yet the results are striking. After 12 months of follow-up in 30 patients and 6 months of follow-up in an additional 15 patients, the authors demonstrate a uniquely stable result. Using the highly sensitive technique of IVUS, only a very minor proliferative response to injury was observed (< 3% luminal volume obstruction)[8]. By angiography, the percent diameter stenosis increased only slightly from a mean of near 10% at the procedure's conclusion to 20% at 1 year[8]. By the 12-month follow-up, not a single patient had sustained clinical or angiographic restenosis[8]. These results are amplified by the recently reported, 238-patient, double-blind, randomized trial in Europe and Latin America, RAndomized, double-blind study with the sirolimus-eluting BX VElocity balloon-expandable stent in the treatment of patients with *de novo* native coronary artery Lesions (RAVEL)[10], which found that restenosis at 6 months was reduced from 26% in patients receiving placebo to 0 in those receiving sirolimus-eluting stents ($p \leq 0.001$)[5]. These dramatic results have created a stir in cardiology. If the present data continue to be supported by ongoing, placebo-controlled, randomized trials [i.e., Sirolimus-Coated BX Velocity Balloon Expandable Stent in the Treatment of Patients with De Novo Coronary Artery Lesions (SIRIUS) in the United States], our patients may finally receive the benefit of a minimally invasive revascularization technique that is also durable.

Limitations

Of course, amid the fireworks, we should maintain our skepticism. The results are very preliminary, the number of patients studied small, the lesions enrolled simple, and the follow-up period still short. Indeed, one patient experienced a myocardial infarction at 14 months. The authors ascribe this to an "unstable plaque" proximal to the stent, but a pessimist might argue that sirolimus eluting from the adjacent stent may have weakened the fibrous cap that protects the underlying lipid pool. Other toxicities may emerge, either from the medication itself or the polymer delivery vehicle. Preclinical trials of stents using different coatings and drugs have reported adverse reactions such as intimal hemorrhage, incomplete healing, intimal fibrin deposition, adventitial inflammation, and medial necrosis. These toxic effects could translate into clinical complications. Aneurysm, pseudoaneurysm, perforation, thrombosis, accelerated atherosclerosis, fibrosis, and systemic disorders are all potential adverse effects of drug-coated stent implants.

Drug-eluting stents may face other challenges. For example, longer-term follow-up may reveal results that are less permanent than anticipated. In fact, in the present study, if one looks critically at the minimal luminal diameter (MLD) changes over the 12-month follow-up period, subtle but noteworthy trends emerge. Two devices were evaluated, the "fast release" coated stents, wherein almost all drug was completely eluted by 15 days, and the "slow release" stent, which uses a polymer topcoat to slow drug release 4 to 6 weeks. In fast release patients, the mean MLD was 2.67 mm immediately after implantation, virtually unchanged (2.69 mm) at 4 months, and then dropped to 2.32 mm (a 13.8% reduction) between 4 and 12 months. Interestingly, in the slow release group (the same formulation that is being tested in the randomized RAVEL and SIRIUS trials) MLD changes occurred over a very different time course. The mean MLD was 2.74 mm immediately after implantation, dropped to 2.55 mm (a 7% reduction) 4 months later, and then dropped only slightly more (2.48 mm, another 2.8% decrease) between 4 and 12 months. Thus, the fast release group demonstrated better efficacy at 4 months, but by 12 months, MLD loss in the fast group had "caught up" to and surpassed that of the slow release group. One wonders if, over a longer follow-up period, an even slower releasing stent would maintain a larger lumen. These data, although subtle and involving small numbers of observations, underscore the need for further follow-up and further development before we fully understand the pharmacokinetics of stent-based drug delivery. Current plans for 18- and 24-month angiographic follow-up in this first group of sirolimus-stented patients will provide important long-term surveillance data[5].

Developing the stent as a drug delivery vehicle posed substantial challenges. The stent's stainless steel struts are poorly designed for drug delivery. Drugs do not bind readily to stent struts and, if bound, the surface area is not very large, providing only a limited drug reservoir. Thus, many researchers turned to stent coatings to facilitate the binding of drugs and to increase the available surface area. The initial stent coatings, however, were dismal failures. In early animal trials, these polymers stimulated an intense inflammatory response, inciting more restenosis. Only recently have biocompatible materials such as methacrylates, polylactides, polyamides, chondroitins, gelatins, and hydrogels, been developed that maintain adequate patency in the animal model. Another challenge was the difficult task of uniformly applying coatings to stent struts (typically accomplished by dipping) and then sterilizing the combination (usually with heat) without altering the properties of the coating or drug. Of course, a safe, biocompatible stent coating must be coupled with an efficacious drug. Manufacturers sprouted new divisions focused entirely on drug delivery to test scores of medications.

Future directions

The sirolimus story implies that we have not seen the end of drug-coated stent development. Indeed, different medicated stents are currently in clinical trials, including 8-Cl-cAMP, simvastatin, paclitaxel, actinomycin-D, c-myc antisense, estradiol, and many others (Table I). Stent coatings have also grown more sophisticated. For example, one novel device uses drugs that are covalently bound to biodegradable "smart" polymers. As the polymer degrades, the drug is programmed to release over months to years. These "designer" coatings can release multiple drugs at different rates on different timelines. Other approaches include absorbent hydrogels applied to the stent surface that can "soak up" and then slowly release antiproliferative medications. Some plans even call on the physician to provide final assembly by dipping the hydrogel-coated stent (like fondue or sushi) into a drug-containing liquid just before deployment. The massive quantity of creative energy being applied to stent-based drug delivery can only improve on the promising results described by Sousa et al.[8,9].

Conclusions

Despite the early nature of this report and the admonition to remain skeptical, it is hard for many of us who have witnessed the growth of interventional cardiology to contain our enthusiasm. The sirolimus-eluting stent will likely be safe and extremely efficacious, and it will soon be joined by other successful drug-coated stents. Its impact on cardiology will probably be at least as important as the impact of stenting itself in the early 1990s. The end of restenosis could be the beginning of

Table I. Ongoing trials on coated stents to prevent restenosis.

Actinomycin-D
Actinomycin-D Pre-Clinical Studies: Evaluation of Dosing, Efficacy and Toxicity
An Advanced c-myc Antisense for Prevention of Restenosis
Angiopeptin: Mechanism of Action and Animal Data
Batimastat: Structural Mechanisms and Animal Studies
Corticosteroids as Anti-Restenotic Agents
The Terumo Statin Releasing Stent - Rationale and Animal Results
Effect of Site-Specific 17beta-Estradiol Delivery on Neointima Proliferation: Mechanisms, Pre-Clinical Data, and the EASTER Trial
The Importance of the Endothelium in the Setting of PCI: Studies on VEGF
Phosphorylcholine Coated Stents As a Drug Delivery Platform
The Conor Medsystems Stent: A Programmable Drug Delivery Device
The RAVEL Trial
The SIRIUS Trial and Rapamycin Registries: Design and Status
Taxol - Preliminary Results of the ELUTES Study
Paclitaxel-coated V-Flex Plus Coronary Stent for Treatment of Recurrent In-stent Restenosis
TAXUS I - IV: Trial Designs, Goals and Enrollment Status
Studies with Actinomycin-D: From ACTION to US OPEN PIVOTAL Study
Study of Anti-Restenosis With the Biodivysio Dexamethasone Eluting Stent (STRIDE)
An Enhanced Site Specific c-myc Antisense Solution to Prevent Restenosis

a new era in revascularization. The old aggressive, "bigger is better" technique will be replaced by a "kinder, gentler" approach achieving an adequate, but more stable lumen, with less procedural risk. Some of the classic "enemies" of percutaneous intervention, such as multivessel disease, diabetic patients[11], left main stenosis, small diameter vessels, long lesions, saphenous vein grafts, bifurcations, and femoral artery disease may well be conquered by drug-eluting stents, leaving chronic total occlusions as the major remaining challenge. Many patients now referred for bypass surgery will likely be candidates for a percutaneous approach. With a stent that does not renarrow, the threshold for intervention may be lowered. For example, as markers for vulnerable plaque are developed, one can envision non-restenosing stents being used to launch a pre-emptive strike against minimally stenotic, yet "at risk" lesions. With their newly acquired ability to suppress intimal proliferation, stents themselves will proliferate.

Physicians and patients can be grateful for the important technological leaps in medicine represented by drug-coated stents. The excitement is well deserved, and our patients will be the beneficiaries. To some it may seem like a dream, but in reality, it just may be sweet dreams for restenosis.

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