Drug-Eluting Stents to Prevent Coronary Restenosis

Szycher M, Ph.D.*; Armini A, Ph.D.; Bajgar C, Sc.D.; Lucas A

* CardioTech International, Inc., 78E Olympia Avenue, Woburn, MA 01801, and Implant Sciences Corporation, 107 Audubon Road, Suite 5, Wakefield, MA 01880.

Copyright 2002. All rights reserved.

Background – The development of coronary stents has revolutionized the practice of interventional cardiology over the past 5 years. More than 70 coronary stents have been approved in Europe and over 20 stents are commercially available in the United States. Unfortunately, epidemiological data shows that 20-25% of coronary stents will restenose. Moreover, in the Stent Restenosis Study (STRESS) certain subsets reached an unacceptably high rate of 30-50% restenosis in patients with diabetes mellitus, long lesions and smaller vessels.

Recent trials have shown that Rapamycin-eluting stents totally prevent restenosis for “de novo” lesions after 2 years. Rapamycin is an immunosuppressive drug, which blocks smooth muscle cell activation and proliferation. It is an FDA-approved drug to prevent kidney transplant rejection.

Methods – The I-Plant™ anti-restenosis stent has been developed as a joint development program utilizing Implant Sciences’ thin film coating and stent technology with CardioTech’s microporous Rapamycin-delivery polymer. The I-Plant stent utilizes a proprietary sustained release ChronoFlex™ polymer that features a programmable and adjustable Rapamycin-elution profile.

Conclusions – We have developed a successful drug-eluting stent designed to inhibit cell proliferation and control the growth of smooth muscle cells. The stent also enhances the “healing” process and regrowth of endothelial cells. Kinetic studies confirm the controlled-release properties of the microporous polymer encapsulation.

Introduction

Stents are now used in approximately 80% of all percutaneous coronary interventions. Although stents were initially used to reduce restenosis after balloon angioplasty in large vessels with focal lesions, interventionalists soon began treating more complex lesions, smaller vessels, bifurcations and thrombosed vessels during the acute phase of myocardial infarction. Most clinicians agree that elective and “bailout” stent use reduces both early complications, and late restenosis compared with balloon angioplasty and other methods of percutaneous coronary intervention.
However, the long-term efficacy of coronary stenting is limited by restenosis, which occurs in 15 to 30% of patients. In-stent restenosis is due primarily to neointimal hyperplasia. Stent-induced arterial injury and the corresponding foreign body reaction incite acute and chronic inflammation of the vessel wall. The inflammatory response, in turn, produces cytokines and growth factors that induce signaling pathways to activate smooth muscle cell migration and proliferation.

**Restenosis after Stenting**

Intracoronary stent implantation has been unequivocally shown to reduce the frequency of in-stent restenosis in focal lesions in relatively large coronary vessels. But, as stents are used in smaller, more tortuous vessels, more complex lesions, and longer stent lengths, the restenosis rates increase alarmingly. Based on a meta-analysis using quantitative coronary angiography, de Feyter conclusively showed that the expected 6-month restenosis rate can be accurately predicted by in-stent minimal area (which is inversely proportional to restenosis) and stent length (which is directly related to restenosis) both of which can be read from a reference chart.

<table>
<thead>
<tr>
<th>Table 1 Factors leading to higher stent thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological</strong></td>
</tr>
<tr>
<td>Small vessels</td>
</tr>
<tr>
<td>Longer vessels</td>
</tr>
<tr>
<td>Multiple vessels</td>
</tr>
<tr>
<td>Pre-existing thrombus</td>
</tr>
</tbody>
</table>

In an effort to reduce restenosis, investigators have tried many drugs incorporated into stents, or “active” stents. Categories can be divided into: (i) anti-inflammatories, (ii) metallocproteinase inhibitors, (iii) NO donors, (iv) anti-sclerosing agents, (v) anti-proliferatives (vi) anti-neoplastics and (vii) “molecular” approaches (genes, cells, anti-sense). We have elected to use Rapamycin (Rapamune, Sirolimus) as our drug of choice, for the reasons outlined in the subsequent paragraphs.

**Rapamycin-eluting I-Plant™ Stents**

The coronary artery response to stent implantation leads to a complex and largely predictable sequence of events. The events are related to inflammation and repair processes, which are known to be natural compensatory mechanisms. The temporal sequence of events to stent implantation can be divided into acute and chronic phases. In the acute phase, thrombosis disturbances predominate. In the chronic phase, tissue remodeling reaches primacy. Thus, while thrombosis takes place early and at the vessel lumen boundary during the acute phase, neointimal hyperplasia and restenosis are protracted in duration, and deeper into the vessel wall during the chronic phase. Interestingly, neither oral anticoagulants, anti-inflammatoryies, or anti-proliferative drugs have prevented restenosis. It is now clear that the most effective pharmacological support to prevent restenosis is the controlled-release of anti-proliferative drugs directly to the target vessel tissue.
Rapamycin (also known as Sirolimus) is an excellent candidate for the treatment of AV graft stenosis since it has been shown to significantly reduce in-stent restenosis and prevent chronic organ rejection. Rapamycin is a natural macrocyclic lactone with immunosuppressive properties, approved by the FDA in 1997 for the prophylaxis of renal transplant rejection. It has been shown to block T-cell activation and smooth muscle cell proliferation. Most importantly, Rapamycin does not inhibit the endothelialization of the intima. Because of its lipophilicity, the drug penetrates cell membranes enabling intramural distribution and prolonged arterial wall penetration. Furthermore, cellular uptake is enhanced by binding to the cytosolic receptor, FKBP 12, which also may enhance chronic tissue retention of the drug.

We have developed a family of rapamycin-eluting stents intended to prevent in-stent restenosis. Rapamycin is a naturally-occurring macrolide antibiotic produced by the fungus *Streptomyces hygroscopicus*, found on Easter Island. The name is derived from Rapa Nui, the native name for Easter Island. Rapamycin is a hydrophobic synthetic drug, FDA-approved as an oral immunosuppressive agent used to prevent organ transplant rejection.

Rapamycin is a potent inhibitor of cytokine and growth factor-mediated smooth muscle cell proliferation. Being a hydrophobic drug, it dramatically increases local (vessel wall) concentrations, while allowing exquisite control over release kinetics. Because local drug concentrations are inextricably linked to biological effects, and not mere proximity, rapamycin appears as an ideal anti-restenotic drug.

Rapamycin exhibits the following pharmacochmical advantages:

- Cytostatic, not cytotoxic
- Readily diffuses across vascular tissue
- It achieves high local tissue concentration
- Inhibits key target cell cycle
- Long half-life in tissues
- Inhibits inflammation by blocking local cytokines
- Potent (only microgram doses required)
- Safe in humans at blood concentrations far exceeding dose delivered from stents

In summary, the ideal drug eluting stent should display the following characteristics:

<table>
<thead>
<tr>
<th>Effective suppression of initial growth</th>
<th>Encourage arterial healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Antithrombotic</td>
<td></td>
</tr>
<tr>
<td>- Anti-inflammatory</td>
<td></td>
</tr>
<tr>
<td>- Anti-proliferative</td>
<td></td>
</tr>
<tr>
<td>- Non toxic to cells</td>
<td></td>
</tr>
<tr>
<td>- Only multiplying cells should be targeted</td>
<td></td>
</tr>
</tbody>
</table>
In-Vitro Drug Elution Studies

The Rapamycin elution kinetics were evaluated from both the solid low porosity sheet and a high porosity, totally encapsulated stent. The work was performed by ProteinLabs of San Diego, California, a commercial protein synthesis and characterization laboratory, using HPLC equipped with a UV detector.

The elution media was calf serum. This choice allowed for a simplification of the elution protocol: the half-life of Rapamycin in serum is longer than in plasma, and the high solubility of the drug in serum eliminates the concerns with reaching equilibrium concentrations prior to changing the elution media.

The results of Rapamycin elution from a low porosity Chronoflex sheet and from a high porosity encapsulated stent containing approximately 217 micrograms of Rapamycin are presented below. The data points represent values obtained in a fresh media, the volume of which was kept constant throughout the experiment.

![In-Vitro Drug Elution](image)

In-Vitro Elution Characteristics of Rapamycin in Serum, measured by HPLC. The experimental data points represent elution from a polymer containing approximately 109 microgram Rapamycin per mg polymer.

It can be seen that the elution of Rapamycin over a period of several days is relatively higher from the high porosity encapsulated stent; the amount of the drug released is thus proportional to the total surface from which the drug is released.
Stent-based drug delivery is a complex therapeutic modality, dependent upon device, drug and tissue properties. The amount of drug that can be loaded or released from a stent is determined by the mode of drug attachment\textsuperscript{[23]} and by stent configuration as shown in Table 2 below:

Table 2

<table>
<thead>
<tr>
<th>Drug immobilization</th>
<th>Drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent type</td>
<td>Geometry and surface area</td>
</tr>
<tr>
<td>Drug loading process</td>
<td>Coating technology</td>
</tr>
<tr>
<td>Bioactivity</td>
<td>Release kinetics</td>
</tr>
</tbody>
</table>

The biological activity of any drug is a function of dose/distribution within the target tissue. Stents cover about 10-15% of vessel luminal surface, thus severely limiting the surface area available for drug loading and release. A delicate balance exists between drug release kinetics and drug diffusion and distribution; drug elution is maximal at points adjacent to the struts, and increasingly lower levels at points progressively further from the struts, creating an uneven activity distribution. Thus, stents made from struts that are spaced far apart produce drug-starved areas, while stents spaced close together will produce areas of overlap.

The I-Plant\textsuperscript{TM} anti-restenosis stent is totally encapsulated in a microporous polyurethane elastomeric mesh. Since the polyurethane is pre-loaded with rapamycin, and all struts are equally covered, the drug distribution pattern into the vessel tissue is even and uniform.

**ChronoFlex\textsuperscript{TM} Polyurethane**

The biocompatibility of the polymer used for coating the carotid stent is crucial. The polymer must be non-inflammatory, capable of being stretched without flaking or delaminating from the stent, and be able to deliver the drug at a sustained, controlled and predictable rate. Very few polymer systems can meet these requirements. For example, most biodegradable polymers, such as polyglycolic-polyactic acid, polyethyleneoxide-polybutylene terephthalate, and polyorthoester showed marked inflammatory reaction.\textsuperscript{24} Non-degradable polymers, such as Biogold polyamine-heparin, and methacryloyl-phosphorylcholine-laurylmethacrylate were acceptable, but polycaprolactone, polyethylene terephthalate, silicone and “polyurethane” showed less than optimal biocompatibility.\textsuperscript{25} Unfortunately, the authors did not specify which “polyurethane” they used. Polyurethanes are not just polyurethanes.

ChronoFlex vascular grafts (5mm ID) were tested in animals over a period of 36 months. The grafts were implanted in adult beagle dogs weighing approximately 25 kgs in a bilateral abdominal aorta to iliac artery position. The dogs were followed monthly by ultrasound to ascertain patency. After elective sacrifice, the grafts were sectioned and stained. Results are shown below:
Chronoflex poly(carbonate)urethane is now the “gold standard” of biodurable polyurethanes, designed for long-term implantation. ChronoFlex is a patented elastomeric polymer synthesized at CardioTech. ChronoFlex is currently used in the CE-marked VascuLink vascular access graft (CardioTech International, Ltd), in the FDA-approved VascuLink (Bard Access Systems), Wallstent Stent-Graft (Schneider-Boston Scientific), intraluminal stents (Schneider), woven grafts (Cordis), orthopedic devices (Howmedica International), heart valves (Aortech Europe Ltd.), self-expanding endoluminal prosthesis (Boston Scientific), sleeves for stent delivery (SciMed Life Systems), finger joints (Howmedica International, Inc.), and coronary artery bypass grafts (CardioTech International Inc.).

**Experimental**

The experimental part of this work consisted of three steps: (1) incorporating Rapamycin into ChronoFlex polymer, (2) low and high porosity samples preparation, and (3) the drug elution studies.

Rapamycin is soluble in several solvents. They include DMSO, acetone and chloroform. The initial experiments were performed by dissolving variable amounts of the drug in DMSO. For ease of removing the excess solvent from the polymer-drug solution we have used DMSO with acetone. After solubilization of the Rapamycin and polymer, we prepared two types of samples:

1. low porosity, low surface area solid sheets and electrosprayed membranes
2. high porosity, high surface area totally encapsulated stents.

The reported data is for the samples containing approximately 109 micrograms of Rapamycin per mg of polymer. The solid sheet was prepared by spreading the mixture over a flat surface from which it could be easily removed. The low porosity membranes and the high porosity, high surface area encapsulated stents were prepared by modified electrospraying. Fig 3 shows an example of a low porosity electrosprayed membrane.
Fig 4 A thru D) are examples of high porosity encapsulated stents, viewed at two different magnifications.

Fig. 3    Low porosity low surface area membrane at 200x.

Fig 4A. 10x Encapsulated expanded and unexpanded top illumination.

Fig 4B. 10x Encapsulated expanded and unexpanded metal stent, top illumination.

Fig 4C. Encapsulated, expanded stent, top illumination 60X.
References


22 Farb A. Comparative pathology of drug eluting stents: insights to relative safety and efficacy. TCT Expert Presentations.
