

Drug-Eluting Stents in Peripheral Vascular Disease: Eliminating Restenosis

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Abstract

Transcatheter endovascular therapy for peripheral atherosclerotic disease has become more popular. In general, good results have been reported in focal aortoiliac disease. However, the long-term patency of angioplasty in longer, more distal lesions has been less satisfactory. Stenting has not been shown to improve long-term patency compared to angioplasty alone. Drug-eluting stents have shown promise in preventing coronary restenosis, and preliminary results in peripheral arterial disease are encouraging. This review article will discuss the current status of endovascular therapy of aortoiliac and femoropopliteal atherosclerotic disease, the theoretic and experimental basis for the use of drug-eluting stents, and the preliminary results in human studies.

Key Words: Drug-eluting stents, peripheral artery occlusive disease, restenosis.

Introduction

RESTENOSIS is the Achilles heel of endovascular therapy for occlusive disease. Immediate technical success of percutaneous angioplasty and stenting for aortoiliac and superficial femoral artery disease is upwards of 90% (1, 2). However, acute occlusion in the periprocedural period and late restenosis have limited long-term patency. While stent placement may decrease the risk of long-term failure in aortoiliac disease, it has not improved long-term patency rates over balloon angioplasty alone in superficial femoral artery disease, possibly due to an increase in neointimal hyperplasia (1–3). Therapy aimed at preventing restenosis may be the key to achieving good long-term results with endovascular techniques.

The response of the artery to balloon dilatation can be divided into four phases, each of which contributes to restenosis:

- the mechanical phase, which may be complicated by early elastic recoil;
- the thrombogenic phase, which is characterized by mural thrombus formation secondary to local hemorrhage and thrombosis;
- the proliferative phase, which is typified by neointimal hyperplasia;
- the remodelling phase, with pathologic changes in the cellular and protein content of the media and adventitia (4).

Stenting has largely eliminated elastic recoil as a cause of restenosis. Therapeutic anticoagulation and antiplatelet therapy are used to prevent thrombosis. Currently, numerous antiproliferative agents, including sirolimus, are under investigation for the prevention of neointimal hyperplasia as a cause of late restenosis.

Sirolimus is a hydrophobic product of the actinomycete *Streptomyces hygroscopicus*. It was initially discovered as an antifungal agent, but was never used because of its immunosuppressive effects. The FDA finally approved it for use as an immunosuppressant in 1999. As a hydrophobic drug, it passes directly through the cell membrane to bind to cytosolic FK506 binding proteins (FKBP). This binding then increases the levels of p27, a ubiquitous cyclin-

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dependant kinase inhibitor, which ultimately interrupts progression of the cell cycle from G1 to S phase (Fig. 1). Medial vascular smooth muscle cells are quiescent (G0). In response to injury, they enter the G1 phase. Sirolimus has been shown to inhibit cell-cycle progression in a variety of cells, including fibroblasts, endothelial cells, smooth muscle cells. Animal studies have shown the maximum rate of proliferation to occur within three to seven days of angioplasty (4). Sustained release of sirolimus from coated stents was confirmed for up to 28 days in a rabbit iliac model, with levels in the blood being undetectable at 2 days. The reduction in neointimal hyperplasia was dose dependent (5). Pharmacokinetic modelling of stent based drug delivery systems suggests that hydrophobic drugs achieve higher mean tissue concentrations and remain closer to the intima. (6). They are also less prone to diffusive backwash into the circulation. This may explain why hydrophobic drugs such as sirolimus and paclitaxel have shown more success in limiting restenosis than hydrophilic drugs such as heparin.

Early results with sirolimus coated stents in human coronary arteries have been impressive. The RAVEL study, a randomized clinical trial comparing a sirolimus coated stent with a standard (uncoated) stent, showed restenosis of 50% or more in none of those receiving treatment but in 26.6% of those in the control group ($p < 0.001$) (7). The difference in stenosis correlated with a significant increase in the rate of major cardiac events in the uncoated group.

Such promising results in the coronary circulation led to the investigation of drug-eluting stents in peripheral occlusive disease (Figs. 2, 3). The SIROCCO (Sirolimus Coated Cordis SMART Nitinol [nickel-titanium polymer] Self-expandable stent for the treatment of Obstruc-

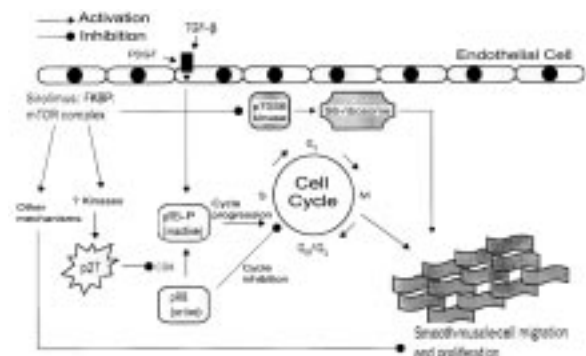


Fig. 1. Artist's drawing of the cell cycle inhibitory events associated with sirolimus therapy for the suppression of neointimal hyperplasia.

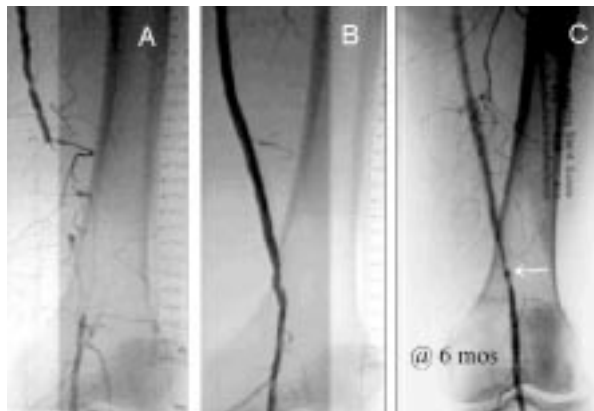


Fig. 2. Superficial femoral artery occlusive disease. (A). A 12 cm long total occlusion of the superficial femoral artery is seen on this contrast angiogram. (B). Following recanalization and balloon angioplasty and stenting, circulation is re-established to the lower extremity. (C). Six months following stent implantation, in-stent restenosis is seen (arrow).

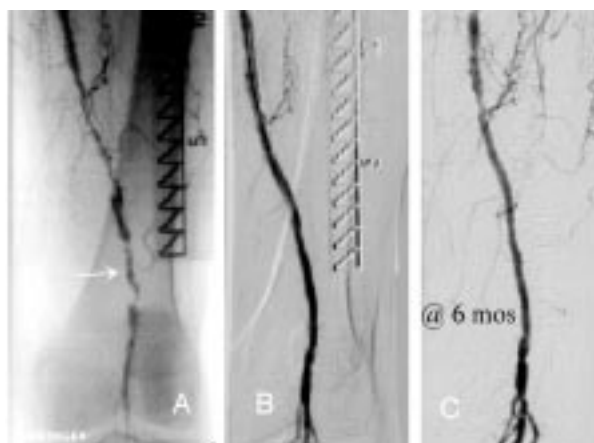


Fig. 3. Superficial femoral artery occlusive disease. (A). Contrast angiogram of a long segment showing stenosis (arrow). (B). Following balloon angioplasty and implantation of a sirolimus coated stent, arterial continuity is restored. (C). Six month follow-up angiogram of same patient as shown in panel B. No in-stent restenosis is seen.

tive Superficial Femoral Artery Disease) study is a multicenter, feasibility study looking at the use of drug-eluting stents in superficial femoral artery disease (8). Thirty-six patients were enrolled in a double-blinded, randomized, prospective fashion. Sirolimus and a co-polymer were bonded in a thin, uniform layer (5–10 &M) to a Cordis SMART nitinol self-expanding stent. The final drug dose was 1.2 mg/stent, and the stents were 6–7 mm in diameter and 8 cm long. Inclusion criteria were symptomatic ischemia, unilateral superficial femoral artery (SFA) stenosis or occlusion, stenotic lesion length between 7 and 20 cm or occlusion be-

tween 4 and 20 cm, a limit of three stents to correct the lesion, and a patent popliteal artery. Exclusion criteria were tandem lesions, poor inflow, scheduled revascularization of the same limb within 30 days of stenting, a previous stent at same site, requirement for stenting of popliteal artery, presence of proximal vascular prosthesis, an aneurysm of the superficial femoral or popliteal artery. The primary endpoint of the study was in-stent percent mean diameter stenosis measured with quantitative angiography at 6 months. Secondary endpoints included: restenosis rate as measured by angiography and duplex ultrasound; ankle brachial indices; hemodynamic failure; Rutherford classification; pharmacokinetic sampling for Sirolimus; the incidence of procedure or stent-related adverse events; and quality of life. Patient characteristics were similar, except for the fact that 100% of the sirolimus treated vessels were calcified, whereas only 47% of control vessels were calcified ($p=0.002$). Both groups had similar baseline angiographic characteristics. Follow-up was complete in 16 sirolimus lesions and 17 control lesions. Patients treated with sirolimus had a significantly greater mean stent diameter seen at 6 months than the control group (4.95 mm vs 4.31 mm). No occlusion, in-lesion restenosis, or in-stent restenosis was seen in the sirolimus group, compared to one occlusion, four in-lesion restenoses, and three in-lesion stenoses in the control group. These findings were not statistically significant.

Conclusions

Primary stenting for peripheral occlusive disease of the femoropopliteal segment has not yielded better long-term outcomes than balloon

angioplasty alone. The initial improvement in technical success seen with stenting is counterbalanced by an increased incidence of neointimal hyperplasia. As such, stenting has been seen primarily as a rescue therapy for failed angioplasty. However, with the advent of sirolimus-eluting stents and their early success in treating obstructing lesions of the superficial femoral artery, stenting may ultimately assume a role as first-line therapy. Further clinical trials with larger groups of patients are warranted.

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