Drug Eluting Stents

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Stenting has reduced the need for clinically driven repeat revascularization, but has far from eliminated it. Restenosis varies from 10 to as high as 50% depending upon the vessel diameter and the length of the lesion, and is higher in diabetics as compared to non-diabetics. The neointimal growth consists of smooth muscle cells (SMCs) in a proteoglycan and collagenous matrix derived from the medial SMCs, which convert from the contractile state to a secretory state leading to cellular proliferation and migration from the media into the intima. These processes are controlled by the complex interaction of cytokines and growth factors. Blockade of any one factor is often insufficient to inhibit the restenosis cascade and therefore attention has focused on disrupting the cell cycle and the inflammatory stimulus to prevent restenosis.

Antineoplastic or immunosupressive drugs are now being incorporated into non-biodegradable and biodegradable polymers applied on stents (rapamycin, paclitaxel, and actinomycin-D). Animal studies in the pig and rabbit coronary and iliac arteries respectively have shown neointimal inhibition at one month. However, the beneficial effects of all three drugs are associated with presence of fibrin deposition occupying 30 to 70% of the neointima. Paclitaxel and actinomycin D are also associated with greater inflammatory infiltrate. Thus showing some delay in healing of the neointima with all three drugs. It is not surprising that once the drug is fully eluted from the stent the vessel begins to heal and long-term studies in animals (3 to 6 months) would be negative for reduction in neointima; which has been shown for rapamycin and paclitaxel eluting stents.

Preliminary results at 6 months from the RAVEL (rapamycin, Cordis J&J) and ASPECT (paclitaxel, CooK) trials have shown a 0% and 4% restenosis, respectively. Why do these drugs lead to a significant reduction in restenosis? Both the drugs are known to act on the cell cycle and reduce the rate of cell proliferation however, rapamycin has the added benefit of also inhibiting T lymphocyte activation and proliferation to antigenic and cytokine (Interleukin 2, 4, 15) stimulation. Paclitaxel is a novel microtubular agent that promotes the assembly of microtobules from tubulin dimers and stabilizes microtubules by preventing depolarization. The microtubule network is essential for the interphase and mitotic cellular function in the cell cycle. Paclitaxel also prevents migration of smooth muscle cells in a dose dependent manner. Actinomycin-D has been shown to have antineoplastic and cytotoxic effects by binding DNA and inhibiting RNA synthesis, respectively. Then why are animal studies negative at 3 and 6 months when studies in man show neoinmal reduction? I believe that human arteries take longer to heal than animal arteries and that long-term follow-up in man following placement of drug eluting stents will be negative.