DRUG ELUTING STENTS – A PANACEA?

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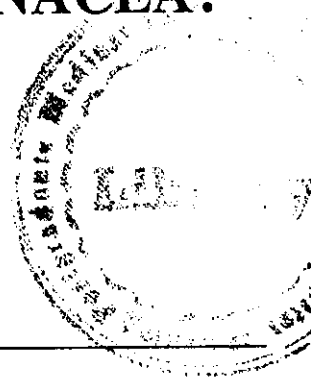

Stents have taken care of many of the acute threatening complications and have opened a new dimension in interventional cardiology.[1] However restenosis remains a monster to be conquered and remains the Achilles' heel of angioplasty. Restenosis is essentially due to recoil and neointimal hyperplasia (NIH). Where as recoil has yielded to the metallic scaffolding, neointimal hyperplasia remains unconquered![2] Restenosis rates after stenting are thought to be between 15 and 25%. While this is clearly better than the rates after balloon angioplasty, the rates may be much higher in less than ideal settings.[3-5]

Many strategies have been devised to decrease neo intimal hyperplasia and hence restenosis rate. There have been a number of recent developments to try and make the stent either non-responsive or to inhibit the tissue response to the stent decreasing neo intimal hyperplasia. Treatment such as atherectomy were proposed on the basis of tissue de-bulking but benefit has not been demonstrated in the recently published data.[6] One current therapeutic strategy is to deliver either β or γ radiation therapy to stented artery and this has, in number of important trials been shown to reduce intimal tissue responses.[7] Current proposals are to either to treat prophylactically those patients known to have a high risk of in-stent restenosis (diabetic, small vessels), but to wait until restenosis occurs in those with lower risk and administer the brachytherapy following restenosis. It is not regarded as necessary nor good practice to treat all those at low risk since therapy would be given to 100 patients to prevent restenosis in 10-15%. Other problems with the use of brachytherapy include the delayed re-endothelialisation that occurs due to radiosensitivity, which in turn can increase the risk of stent thrombosis.[8]

The dream of all interventional cardiologist was to have a stent without restensois. In an effort to reduce restenosis, investigators have tried many drugs to coat the stents and render them "active" stents. The systemic and local delivery of different agents have been tried to suppress neo intimal hyperplasia. Stents have been coated with antiinflamatory, anti proliferative and antimigratory drugs to achieve desirable results. Sirolimus (rapamycin), Paclitaxel, Actinomycin D and many other agents have been tried to inhibit cytokine-mediated and growth factor proliferation of lymphocytes and smooth muscle cells to reduce neo intimal proliferation.[9,10]

Drug eluting stents (DES) have come in with the bang but whether the they will be able to sustain the 'reputation' remains to be seen! In this article we will discuss the

targets of anti restenosis, the evidence in support of new agents and DES, the effects of new DES, the caveats and realities and the future directions in the world of interventional cardiology.

Cellular and molecular targets for anti restenosis therapy:

Changes of neointima include cell migration and proliferation that contribute to the development of restenosis. The earliest stage of proliferation actually take place in the adventitia where migration of smooth muscle cells contribute to negative remodeling. The medial smooth muscle cells have a wide functional capacity. They carry alpha, beta and dopamine surface receptors and thus are involved in signal transduction, have functional contraction and force generation and proliferate to form restenotic tissue. Potentially triggered by unclean techniques, such as finger touching of the balloons and wires, are important components of the process. It is certainly undesirable for these cells to be destroyed as happens during radiation therapy and after high dose drug elution, e.g. Actinomycin D application. The thin endothelial layer is probably less important in the pathogenesis of restenosis; it is entirely denuded during balloon inflation's. More important appears to be the mechanical rupture of the lamina interna. Thus the molecular targets of interest are the cell cycle and cell proliferation, the synthesis of collagen and extra cellular matrix.[10,11]

Among currently evaluated drugs, sirolimus is a naturally cell cycle inhibitor antibiotic found exclusively on the Easter Islands. It inhibits growth factors or cytokine stimulated cell proliferation The action of paclitaxel is multifunctional, interrupting multiple pathways altering the dynamics of micro tubular function on many levels. It inhibits G2 phase of the cell cycle and at high doses causes mitotic arrest and apoptosis. Actinomycin D at high doses causes media necrosis, underlying the toxic potential of these drugs. Thus the ideal drug-eluting stents has anti thrombotic, anti inflammatory, anti proliferative and non-toxic properties. Thus current treatment strategies could be complemented with systemic drug booster doses. A study demonstrated improved healing after a single booster injection after 28 days.[12]

Sirolimus eluting stent:

Naturally occurring antibiotic was approved by FDA in 1999 for renal transplantation. It inhibits growth factors or cytokine stimulated cell proliferation. It prevents vascular hyperplasia in all grafts and angioplasty models. It readily diffuses across the vascular tissue. It also inhibits proliferation and inflammation. Receptor FKBP is up regulated in smooth muscle cells and helps in the antirestenotic effect of sirolimus.[13] The sirolimus eluting stents is balloon expendable, stainless steel with thin uniform coating (5-10 Um). Only 3% (180 ug) of Rapamycin is released from the coronary stents daily.[14]

The 2 years follow-up data of sirolimus stents implantation first (FIM) with 30 number of patients is very good. At the end of 2 years no death, one (3.3%) Q wave MI, one (3.3%) TVR (CABG), one (3.3%) TLR (PCI) and event free survival was 90% in 27 patients. The early clinical benefits (4 months) observed after Sirolimus Bx-velocity appear durable at late follow-up (2 year). In most of the patients neointimal hyperplasia continued to be minimal and the lumen was well preserved up to 2 years (late-loss: FR 0.32 mm; SR-0.09 mm). No aneurysm, pseudoaneurysm, perforations or other systemic disorders were observed. At 2 years follow up, sirolimus eluting stents continues to be a major breakthrough in the fight against restenosis.[15]

RAVEL study was the first randomized, double blind, controlled trial demonstrating sustained, predictable clinical benefit of a drug eluting stent upto 1 year. RAVEL study shows treatment of de novo lesion with sirolimus eluting stent is safe. There was no acute thrombosis, or sub acute thrombosis in 30 days. No late stent thrombosis although clopidogrel/ticlopidin was administered for only 2 months. No death related to use of sirolimus eluting stent. At one year follow-up there was absence of re intervention, no clinical evidence of "Catch up" phenomenon. Event free survival at 1 year was 94% and superior ($P < 0.0001$) to the 71% event free survival of control group.[16]

Abizaid reported the results of sirolimus stent (cypher) in the setting of in-stent restenosis in 41 patients. Vessel size was 2.5 – 3.5 mm, one or two – 18mm cyhyper™ stent used. In hospital results were remarkable, with 100% successful stent deployment, no death, MI, emergency CABG or sub acute thrombosis reported. These were maintained at 11 ± 1 months clinical followup. However these findings need to be confirmed by a larger, randomized clinical trial that will be able to define the real impact of this strategy in the treatment of serious condition, in-stent restenosis.[17]

Preliminary interim analysis of the first 400 patients from SIRUS multi centers US. Clinical trial which compared the sirolomus eluting Bx Velocity TM stent to control bare stents in-patients with native coronary lesion. In comparison to previous sirolimus clinical experience outside the U.S. (FIM and RAVEL), enrollment included patients with more frequent cardiac risk factors (esp. diabetes), more complex patients (increased multivessel disease and prior PCI/CABG), longer lesions, and frequent overlapping stents (25%). In stent neointiamal hyperplasia was dramatically reduced (late loss decreased by 85%) resulting in a lowering of in stent restenosis by 94% form 31% in control group to 2% with sirolimus ($P<0.001$). These findings were corroborated in the IVUS subanalysis, which demonstrated a similar reduction in FU in stent neointimal volume and volumetric plaque burden (92% and 90% respectively). Neointimal hyperplasia in the proximal and distal stent margins (Peri stent) was less effectively suppressed by sirolimus (late loss decreased by 38% proximal and 79% distal) resulting in a lowering of in: in segment" restenosis by 72% from 32% in the control group to 9% with sirolimus ($P < 0.001$). Similarly, TVF, the primary endpoint, was reduced by 46% from 19.5% with control to 10.5% with sirolimus ($P=0.016$). Again within the sirolimus group, there was a higher frequency of TLR in small versus larger vessels (8.8% Vs 1.8%), usually associated with proximal margin peri stent restenosis.[18]

Paclitaxel Eluting Stent

Paclitaxel interferes with microtublar dynamics and inhibits microtublar destruction, multiple stages of cell cycle are microtubular dependent. The dose of paclitaxel that is used in these stent is 28000 fold less than doses common in chemotherapy.[19]

TAXUS I is the first efficacy study that evaluates the use in de novo coronary lesions. The 30-day rate of MACE is 0%. In the 6 months QCA analysis the restenosis rate was 0% Vs 10.3% in the stenotic de novo lesion No edge effect was observed. The neointimal volume was reduced by 30% in the drug arm. These results remain equally favorable at 12 months.[19]

TAXUS II is the fiesta efficacy study. 530 patients received either a sequential slow or a moderate release formulation of the stents. Both groups showed very good results. The slow release cohort showed 4.1% MACE, the moderate release cohort 1.4%.[19] The European evaluation of paclitaxel

eluting stent (ELUTES TRIAL) is a dose finding study as a triple blind efficacy and safety trial patients with similar de novo lesion will be randomized to 4 different drug doses and be followed for end point, like percentage diameter stenosis, and safety. In the latest data report diameter stenosis in-patients receiving the highest dose density paclitaxel crated stents was 14%, compared to 44% in the control group ($p<0.01$). Late loss was 0.10mm in the high dose group, compared to 0.71mm in the control group ($p=0.005$). The binary stensois was 3% in the high dose group, compared to 21% in the control group. Major adverse cardiac events did not differ significantly between the groups and no late stent thrombosis was noted. Independent predictors for ISR were DM a higher paclitaxel dose, and the vessel size.[20]

Estradiol eluting stent:

Estradiol may have vascular protective effects. Among many beneficial effects it promotes healing, has anti-inflammatory and anti migration effect. The progression of atherosclerosis is potentially reduced.

Preclinical studies have compared high and low doses. Significant reduction in NIH was seen with high doses. Impressive was the lack of inflammation and fibrin deposition. Further reendothelialization loss not showed. There was no MACE observed at 30 days.[21]

Actinomycin D Eluting Stents

Actinomycin D, acts at all stage of cell cycle. It prevents RNA transcription from DNA. Dose dependent reduction of neointimal hyperplasia and evidence of early healing has been observed. In Action trial, a trial of drug eluting actinomycin D stents, there were no untoward events at 30 days. The rate of MACE at 1.4% matched the event rates of other Guidant trials. At 44 days no fatality was observed at 120 days no QWMI, or NQWMI. However, at angiographic follow up, there was an unacceptably high rate of restenosis. This led to the halt of action trial, as it remained doubtful that the restenosis rate would be reduced. The patients will be followed, but it is unlikely that there will be future studies with actinomycin D.[22]

Caveats, new realities, and cost:

Though most of the trials present a very encouraging picture there are facts to the contrary as well! Late restensosis with a specific drug eluting stents design, at 6 months, the rate of restenosis was 15%, the late loss was 0.47 mm, and TLR was 20%. However at 12 months, the results were much worse: 08 patients had restensois (61%) and the late loss index was 1.6. The drug (taxane) might have lost activity over time, contributing to the changes.[23] The sirolimus stent treatment of in-stent restenosis, study was performed in Saopaolo and Rotterdam. In the Saopolo Cohort, there were promising results. In the Rotterdam cohort there was 2 deaths, 1 NQWMI, 1 total occlusion, and 2 cases of recurrent in-stent restensois.[24] Angiogrpahic followup of Action trial led to the halt of trial due to unacceptably high rate of restenosis.[22]

In Ho's model of restensos, cost saving occurs in diabetics with small vessel and in non-diabetic patients with longer lesion in small vessel. Drug eluting stents are cost effective in moderate to large size vessel in diabetics and longer lesions a vessel under 0.3 mm in non-diabetic patients, but in larger vessel in either group with any increase in mortality, cost effectiveness of drug eluting stents disappears. Restenosis is still important clinical economic factors in U.S. health care system, and direct costs are $ 8000-$28000 per episode or $1500-$8000 per patient. Restenosis adversely affects quality of life and the cost threshold appears to be

$10000 for repeat revascularization avoided within the U.S. health care system. Overall, simulation models show cost effectiveness with drug eluting stent for the majority of patients, with cost saving being confirmed to specific patient population.[25]

Future and challenges for DES.

Study results with 0% complication as in the RAVEL trial will not be repeatable in the real world. However the effect of DES overall will be much more profound than expected.

What will be life after RAVEL ? It would be too simplistic to extrapolate the RAVEL data into general. It is a true breath through technology and DES will become core technology. Patients being treated with CABG or Chronic medication today will be treated with PCI tomorrow and patients will be seen earlier and later than now. Very soon spill over effects into other vascular fields will be seen and PCI will be the gold standard for all significant vascular disease. With wider application of DES multivessel disease, ostial lesion, complex bifurcation will be treated with PCI. However good operator technique will remain supreme IVUS may undergo resurgence. Pre- debulking may prove outcomes. Last but no least, treatment with these new stents will be dependent on cost.[26]

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