Delayed Occurrence of Restenosis in Drug Eluting Stents: An Evidence of Delayed Healing


Abstract
Drug eluting stents have made a significant impact on restenosis. However, there are concerns regarding delayed “catch-up” of restenosis. In this case report we present two such patients with delayed occurrence of restenosis after drug eluting stent implantation.

INTRODUCTION
Drug eluting stents (DES) reduce the incidence of restenosis by inhibiting neointimal hyperplasia. However, reduction in neointimal hyperplasia by DES may also delay endothelialization of stent struts. It is feared that inhibition of complete endothelialization in DES may predispose to higher risk of stent thrombosis. It is also postulated that suppression of neointimal hyperplasia by DES may be temporary and as the drug effect wears off, a “catch-up” phenomenon in restenosis may be observed. Upto 2 years follow up of ‘first in man’ implantation of DES is presently available and does not seem to suggest delayed increase in restenosis. Longer follow up in larger studies, however, is needed to clarify the issue.

CASE REPORT
We have been implanting both sirolimus eluting (Cypher™, Cordis, Europa, NV) and paclitaxel eluting (Taxus™, Boston Scientific, Ireland) stents since June, 2002. As a part of our protocol we are performing follow up angiography in all the patients with DES implantation at 6 ± 1 months of follow up or earlier if symptomatically indicated. We have observed delayed occurrence of restenosis in 2 of our cases (one with Cypher and one with Taxus stent). In both the instances patients were asymptomatic at the time of 6 months follow-up angiography with moderate late loss in the stented segment. On subsequent follow up, both of them became symptomatic and repeat angiography revealed significant progression of disease leading to target lesion revascularization.

Case 1: SKM, a 55 years old male, normotensive, non diabetic, normolipidemic, non smoker presented with unstable angina in September, 2002. His coronary angiography revealed single vessel disease with 90% eccentric stenosis in proximal LAD artery (Fig. 1A). He underwent coronary angioplasty using Taxus 3.0 x 24 mm stent which was postdilated with 3.5 mm balloon. The adequacy of stent expansion was confirmed with intravascular ultrasound (IVUS) evaluation. His final angiogram is shown in Fig. 1B. He was followed up on aspirin, clopidogrel, ramipril and atorvastatin. He underwent follow up angiography 6.2 months after angioplasty which revealed moderate late loss constituting 44% stenosis in the middle of the stent (Fig. 1C). He was asymptomatic at that time and was continued on same medical therapy. He became symptomatic with exertional angina NYHA class II two months later and underwent a treadmill test, which was positive for inducible ischemia. He underwent repeat coronary angiography around 2.5 months after first follow up angiography which revealed marked progression of late loss which now constituted 90% stenosis in the middle of the stent (Fig. 1D). He was treated with repeat angioplasty and stenting using 3.0 x 28 mm Cypher stent. His symptoms were relieved and he is presently symptom free on 6 months subsequent follow up.

Case 2: MJ a 30 years old diabetic patient who had anterior myocardial infarction in June, 2002. He was thrombolysed elsewhere and was referred to us with recurrent post myocardial infarction angina. His coronary angiography revealed totally occluded LAD artery (Fig. 2A). He underwent angioplasty using Cypher 3.0 x 18 mm stent after administering Inj. Abciximab bolus and infusion. His final coronary angiogram is shown in Fig. 2B. He remained asymptomatic thereafter and was on aspirin, clopidogrel, enalapril, metoprolol
and atorvastatin. He underwent routine follow up angiography at 8 months of follow up which revealed 41% stenosis at proximal edge of stent by quantitative coronary angiography (QCA) (Fig. 2C). He was continued on same therapy. He became symptomatic with variable threshold angina 4 months later. His repeat angiography revealed progression of stenosis to 83% by QCA (Fig. 2D). He was treated with repeat angioplasty using another Cypher 3.0 x 18 mm stent which was postdilated with 3.5 mm balloon with good final result. He was continued on same medical therapy and is now asymptomatic at 6 months of subsequent follow up.

**DISCUSSION**

Time course of endothelialization and restenosis in bare metal stent (BMS) has been well documented.\(^2^,\)^\(^3\) Progression of neointimal hyperplasia after 6 months of stent implantation in BMS is rare. Infact, instent neointimal tissue appears to regress after 6 months of BMS implantation.\(^4\) Neointimal hyperplasia in DES does not seem to follow this time course. The timing of peak neointimal hyperplasia in DES is not clearly known. In the present two cases, neointimal hyperplasia was found to be progressive even after 6 months of stent implantation. The occurrence and frequency of such delayed neointimal hyperplasia after DES is presently unknown.

The possible reason of this delayed progression of neointimal proliferation in DES can be due to initial temporary suppression of neointimal growth by the drug with subsequent proliferation when the drug effect wears off. Such a phenomenon does not appear to be universal as is clear from the available follow up data of DES. The factors which predispose to its occurrence, however, remains to be clarified. Similarly, the possible means to prevent its occurrence need to be determined. One of the possible way could be oral supplementation of the similar drug to inhibit neointimal growth for longer duration since the drug from the stent is released completely by 2-3 weeks. This concept is presently being evaluated in various studies with oral Rapamune.\(^5^,\)^\(^6\)

Another issue which emerges from this report is the need of longer follow up after DES as compared to BMS implantation so that the time course of neointimal hyperplasia and the incidence of late stent thrombosis, aneurysm formation and late stent malposition could be evaluated.

**CONCLUSION**

The case report shows that delayed occurrence of restenosis in DES, a “catch-up phenomenon”, is a distinct possibility. It’s incidence, predictors and possible preventive measures need to be elucidated.

**REFERENCES**


### Announcement

**RSSDI – 2005**

**33rd Annual Conference**

**23rd, 24th and 25th September 2005, Bangalore**

The highlights of the Conference include the following:
- The Conference Venue is in the midst of IT icons surrounded by greenery, go-karting etc.
- The Conference building is aesthetically designed to have an excellent acoustics.
- More than 3000 delegates are expected to attend.
- As part of the Conference, CME is also organized.
- Nationally and Internationally acclaimed faculties shall address the delegates using the state-of-the-art audio-visuals.
- Parallel scientific sessions.
- Many pharma companies have agreed to display their products and services.
- The following is the delegate fees:

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* Participation in CME needs a separate registration fee.

- Accommodation, transport and sight seeing shall be arranged on request.
- Accompanying children and spouses shall have fun time at the venue itself.

For further details, please contact: **Dr. KR Narasimha Setty**, Organising Secretary, RSSDI-2005, 132/18, 22nd Cross, III Block, Jayanagar, Bangalore – 560011

Phone: +91-080-57726555; Fax: +91-080-51307737

Email: krnsetty@touchtelindia.net; Web: www.rssdi2005.com

### Announcement

**2nd Infectious Disease Certificate Course - IDCC 2005**

**PD Hinduja National Hospital, Mumbai**

**25th August to 3rd September 2005**

**Eligibility for course**: 0-10 yrs Post MD/DNB in Medicine/Pediatrics/Microbiology

**Focus**: Diagnosis, Management and Prevention of infectious disease

**Format**: Ward Rounds, Archived Cases, Interactive Lectures, Microbiology Discussions, Visits to Infectious Disease Hospital

**Registration fees**: Rs. 3,000/- Cheque payable to PD Hinduja National Hospital and Medical Research Centre. Participants to make their own arrangement for accommodation.

**Last date**: 30th June, 2005

**Contact Number**: 2444 7704/5 (Marketing Department)

**Course Coordinators**

Dr. FD Dastur     Dr. R Soman     Dr. Camilla Rodrigues     Dr. Tanu Singhal