SCIENTIFIC LETTER

Late angiographic stent thrombosis of polymer based paclitaxel eluting stent

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The drug eluting stent (DES) has largely abolished the risk of in-stent restenosis and repeat revascularisation compared with the bare metal stent (BMS). In some parts of the world, DES implantation has been adopted as a default strategy for percutaneous coronary intervention in many centres. However, this enthusiasm was recently weakened by the occurrence of a severe adverse event, late angiographic stent thrombosis (LAST).^{1,2} This newly described entity was presumed to be related to delayed endothelialisation of the implanted DES. We report a case series of LAST involving the polymer based paclitaxel eluting stent (Taxus, Boston Scientific Corporation), all of which occurred after discontinuation of clopidogrel. Importantly, we found that both DES and BMS can be susceptible to LAST when antiplatelet treatment is discontinued.

CASE 1

Patient 1 was a 44 year old man who underwent percutaneous coronary stent implantation for evolved myocardial infarction in September 2002. A 3.0 mm (diameter) × 24 mm (length) Taxus stent was implanted in the proximal left anterior descending coronary artery (LAD). Treatment for six months with aspirin (100 mg/day) and clopidogrel (75 mg/day), followed by life long aspirin (100 mg/day), was recommended. The patient was compliant with antiplatelet treatment but continued to smoke. He remained well until 13 months later when he was readmitted with acute anterior myocardial infarction. Emergency coronary angiography showed a totally occluded proximal LAD at the site of the previously implanted Taxus stent. Intravascular ultrasound (IVUS) showed only mild in-stent neointimal hyperplasia, suggesting primarily a thrombotic event. The stent was well expanded except for a small segment at the proximal stent edge. No stent malapposition or edge stenosis was noted. Balloon dilatation was performed with the elective use of eptifibatide. The patient made an uneventful recovery and was discharged four days after the procedure.

CASE 2

Patient 2 was a 76 year old man who underwent percutaneous coronary stent implantation for evolved myocardial infarction in February 2004. A 2.5 × 24 mm Taxus stent was implanted in the proximal LAD. Treatment for six months with aspirin (100 mg/day) and clopidogrel (75 mg/day), followed by life long aspirin (100 mg/day), was recommended. He was readmitted eight months later with acute anterior myocardial infarction after stopping aspirin for three days because he had run out of medication. Emergency coronary angiography showed a totally occluded proximal LAD stent. He underwent thrombus aspiration with an aspiration catheter followed by balloon dilatation with a non-compliant balloon. The patient made an uneventful recovery and was discharged five days after the procedure.

CASE 3

Patient 3 was a 50 year old man who underwent percutaneous coronary stent implantation for acute coronary syndrome in May 2004. A 3.0 × 28 mm Taxus stent was implanted in the proximal LAD. Treatment for six months with aspirin (100 mg/day) and clopidogrel (75 mg/day), followed by life long aspirin (100 mg/day), was recommended. Although once non-compliant with antiplatelet treatment (he stopped all medications for one month soon after the procedure), he resumed and continued all medications (including aspirin and clopidogrel in the recommended regimen) after being advised by a physician but was readmitted seven months after the initial procedure with acute anterior myocardial infarction. Emergency coronary angiography showed a totally occluded proximal LAD stent. IVUS showed that the Taxus stent was well expanded and apposed to the vessel wall, but there was moderate neointimal hyperplasia at the proximal portion of the stent and significant atherosclerotic disease at the proximal stent margin. Bolus and infusion of eptifibatide was administered. After balloon predilatation, a 3.5 × 16 mm BMS (Liberte stent, Boston Scientific Corporation) was implanted in the proximal LAD lesion, overlapping the proximal edge of the Taxus stent. The patient recovered uneventfully and was discharged four days after the procedure.

CASE 4

Patient 4 was a 51 year old man who underwent percutaneous coronary stent implantation for stable angina in January 2004. A 2.25 × 32 mm Taxus stent was implanted in the proximal LAD and a 3.5 × 18 mm BMS (Bx Sonic stent, Cordis, Johnson and Johnson) was implanted in the mid left circumflex artery during the same procedure (fig 1A–C). Treatment for six months with aspirin (100 mg/day) and clopidogrel (75 mg/day), followed by life long aspirin (100 mg/day), was recommended.

Sixteen months later, he was readmitted for an elective upper endoscopy for investigation of anaemia. The gastroenterologist advised him to stop the aspirin three days before the endoscopy, which turned out to be an uneventful procedure. While in the recovery room, the patient became unwell and developed chest discomfort. A 12 lead ECG showed ST segment elevation over the anterior precordial leads compatible with anterior myocardial infarction. He then developed cardiogenic shock and required endotracheal intubation. Emergency coronary angiography showed thrombosis of both the DES (Taxus, in the LAD) and BMS (Bx Sonic, in the mid left circumflex artery) (fig 1D). Despite successful coronary stenting and achievement of antegrade TIMI (thrombolysis in myocardial infarction) grade 3 flow to

Abbreviations: BMS, bare metal stent; DES, drug eluting stent; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LAST, late angiographic stent thrombosis; TIMI, thrombolysis in myocardial infarction

Figure 1 (A) Baseline coronary angiography showing significant stenosis over the proximal left anterior descending artery (LAD, large arrow) and mid left circumflex artery (LCx, small arrow). Successful implantation of (B) a Taxus stent to the LAD and (C) a bare metal stent (BMS) to the LCx. (D) The patient returned 16 months later with late angiographic stent thrombosis involving the Taxus stent and BMS (dash lines). (E) Successful recanalisation of the Taxus stent.

the LAD (fig 1E), the patient deteriorated rapidly and developed refractory ventricular tachycardia and cardiogenic shock. A resuscitation attempt was unsuccessful.

CASE 5

Patient 5 was a 33 year old man who underwent percutaneous coronary stent implantation for recent myocardial infarction in March 2005. Two Taxus stents (4.0×12 mm, 3.5×32 mm) were implanted in the distal right coronary artery. Treatment for six months with aspirin (100 mg/day) and clopidogrel (75 mg/day), followed by life long aspirin (100 mg/day), was recommended. Because of non-compliance, he defaulted follow up and stopped all his medications including aspirin and clopidogrel five months after the procedure. One week after stopping medication, he was readmitted with acute inferior myocardial infarction. Emergency coronary angiography showed thrombotic occlusion of the Taxus stents at the distal right coronary artery. Intravenous abciximab was administered before emergency angioplasty. A large thrombus was aspirated by a thrombus aspiration catheter (fig 2). IVUS showed that the two Taxus stents were well expanded and apposed to the vessel wall. There was no residual edge dissection and minimal in-stent neointimal hyperplasia. Balloon dilatation with a non-compliant balloon was performed and final TIMI 3 flow was achieved. The patient made an uneventful recovery.

DISCUSSION

DESs have been proved to be highly effective in reducing the in-stent restenosis rate in multiple randomised clinical trials.³⁻⁴ The sirolimus eluting stent (Cypher, Johnson and

Figure 2 A large thrombus aspirated by the aspiration catheter.

Table 1 Summary of the five patients who developed late angiographic stent thrombosis (LAST) after Taxus stent implantation

	Patient number				
	1	2	3	4	5
Risk factors	HC, FH, smoker	HT	HT, HC, former smoker	DM, HC	Smoker
Stent size (diameter × length) (mm)	3.0×24	2.5×24	3.0×28	2.25×32	4.0×12, 3.5×32
Target vessel	LAD	LAD	LAD	LAD	RCA
Indication	Recent MI	Recent MI	ACS	Stable angina	Recent MI
Aspirin stopped	No	3 days, ran out of medication	No	3 days, for upper endoscopy	7 days, non-compliance
Clopidogrel stopped	Finished	Finished	Finished	Finished	Non-compliance
Time to LAST (months)	13	8	7	16	5
Treatment	BA	BA	Stenting	Stenting	BA
Outcome	Alive	Alive	Alive	Dead	Alive

ACS, acute coronary syndrome; BA, balloon angioplasty; DM, diabetes mellitus; FH, family history of coronary artery disease, HC, hypercholesterolaemia; HT, hypertension; LAD, left anterior descending coronary artery; MI, myocardial infarction; RCA, right coronary artery.

Johnson) and polymer based paclitaxel eluting stent (Taxus, Boston Scientific Corporation) are the two DESs approved by the US Food and Drug Administration for clinical use. In contrast to BMS, for which dual antiplatelet treatment for four weeks is recommended after stent placement, endothelialisation of the implanted DES was observed to be delayed in animal studies.⁵ Consequently, a prolonged course (six months) of dual antiplatelet treatment is recommended after Taxus stent implantation.

LAST, defined by angiographic evidence of stent thrombosis associated with acute symptoms more than 30 days after DES implantation, was recently described.^{1,2} This phenomenon is extremely rare with BMS except after vascular brachytherapy, which delays the process of stent strut endothelialisation. Little information exists regarding LAST after DES implantation; data on the incidence, predictors, treatment, and outcomes are eagerly awaited.

Up to 31 March 2005, in our institution 1287 Taxus stents were implanted in 594 patients. On the basis of this sample, the incidence of LAST was 0.8% (five of 594). Among the five cases in the present report (table 1), we observed that with the exception of patient 5, who discontinued the medication due to non-compliance, none of the LAST occurred within the first six months when the patients were still treated with dual antiplatelets. Our data, together with a report by another group,^{1,2} suggest that the time frame for LAST to occur after Taxus stent implantation was between 5–18 months. In this reported series, LAST occurred regardless of whether a patient was taking or had discontinued aspirin. This observation is shared by the Rotterdam group.^{1,2} This suggests that, at least for the Taxus stent, aspirin monotherapy after six months may not be totally effective in preventing stent thrombosis and that aspirin should not be stopped without a good medical indication.

It is intriguing that in all other reported series,^{1,2} either only a DES was implanted in the original procedure or, if both a BMS and a DES were implanted, only the DES developed thrombosis, whereas the BMS remained patent. This raises the concern that DES is more susceptible to LAST. In this regard, our patient 4 provides unique insight because the DES and BMS were implanted in different vessels in the original stenting procedure. This is the first time we have

observed both DES and BMS developing thrombosis after aspirin was stopped. We suspect that, for certain patient subsets, the process of endothelialisation may be significantly delayed even after BMS implantation. As a result, in these patients, both DES and BMS are susceptible to LAST under vulnerable conditions such as when aspirin is discontinued. Lastly, for patients who developed LAST despite good compliance with antiplatelet treatment, aspirin or clopidogrel resistance, or both, may have contributed to the event.

In summary, LAST is a phenomenon that deserves special attention after DES, especially the Taxus stent, implantation. We suggest a more prolonged period of treatment with dual antiplatelets (up to 18 months) than currently recommended. Every effort should be made to ensure good compliance with antiplatelet treatment and these medications should not be stopped lightly.

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