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Successful local antiproliferative paclitaxel delivery in a repeatedly restenosed lesion of the right coronary artery after drug eluting-stent implantation

Sirs: We present the case of a patient with symptomatic severe coronary 3-vessel disease, who has been treated with repeat PTCA, stent implantation and even repeat drug-eluting stent implantation of the same lesion in his right coronary artery without lasting success. Since implantation of a CYPHER^{TM} stent (Cordis, Johnson & Johnson) as well as a TAXUS^{TM} stent (Boston Scientific) led to significant and symptomatic in-stent restenosis within 3 months, the patient was then admitted to our institution and scheduled for coronary artery bypass graft (CABG) surgery. However, since his subtotally restenosed RCA was currently the only lesion that needed treatment, it was discussed with the patient to perform a catheter-based local delivery of paclitaxel via the newly developed GENIE^{TM} catheter (Acrostak Corp., Winterthur, Switzerland) for restenosis prevention (see Fig. 1). The intervention was primarily successful, and repeat coronary angiography after 3 and 9 months showed no new restenosis formation.

A 57-year old patient with known severe coronary multivessel disease was admitted to our institution because of typical effort-induced angina pectoris. In his history he revealed a subacute inferior myocardial ST-elevation infarction in 2004 and underwent

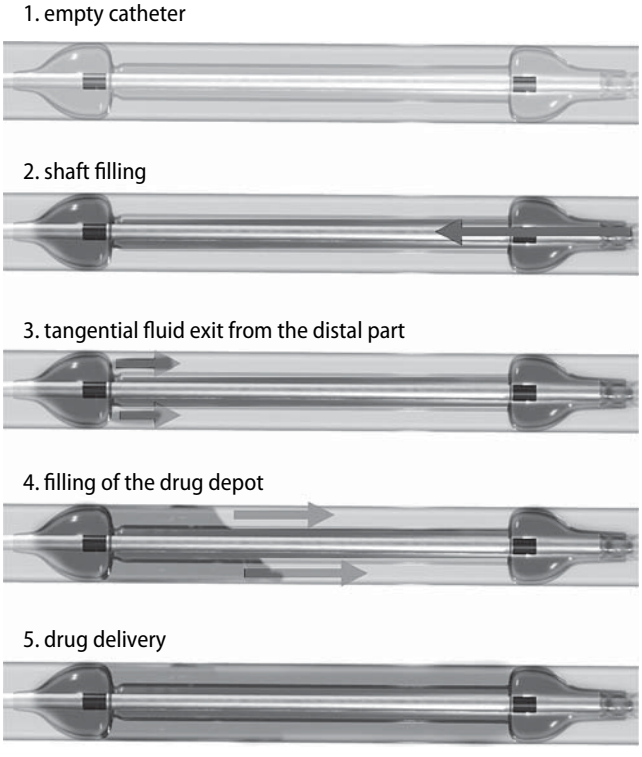

Fig. 1 Schematic drawing: function and aspect of the application device for local drug delivery

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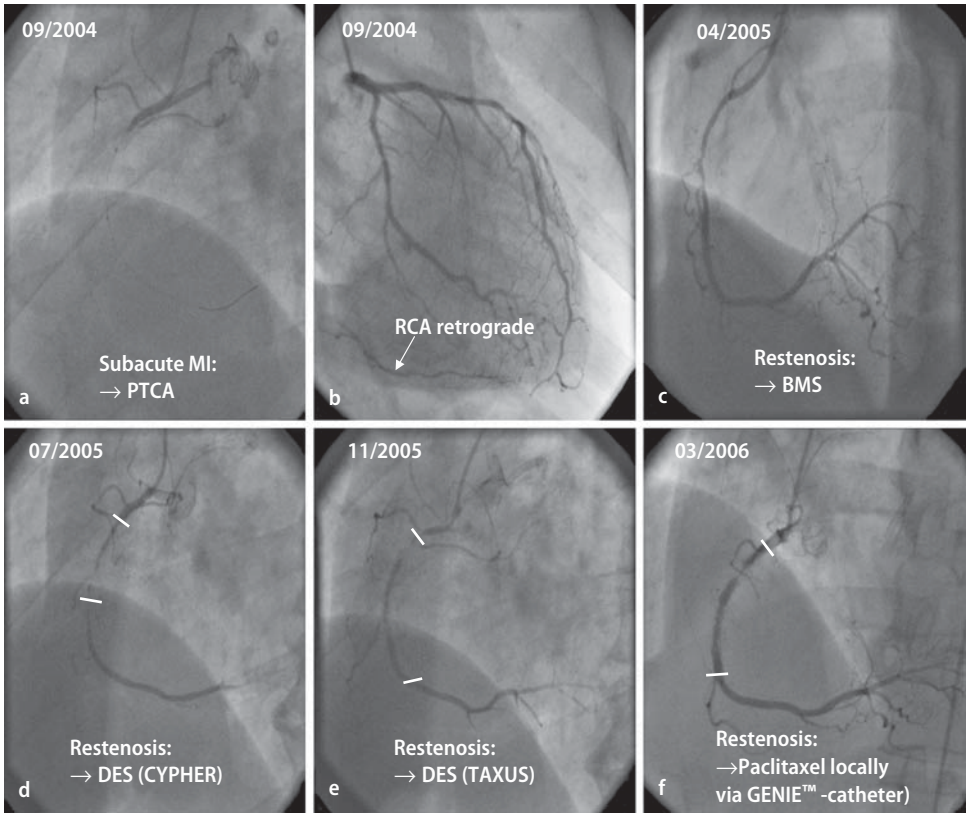

Fig. 2 Angiographic findings after initial subacute posterior myocardial infarction (**a**, **b**). Repeated restenosis within a few months after PTCA (**c**), implantation of a bare metal stent (**d**), CYPHER stent (**e**), and TAXUS stent (**f**). Bars represent the borders of the last stent that was implanted

PTCA of the functionally occluded RCA. Six months later he underwent repeat coronary angiography because of *de novo* angina pectoris and had stenting (bare metal stent, BMS) of the LAD because of progression of his coronary artery disease (CAD), as well as stent implantation in the RCA because of restenosis (BMS). Three months later a CYPHER^{TM} stent was implanted in the RCA because of symptomatic in-stent restenosis, and 1 month later a CYPHER^{TM} stent was implanted in the LAD as well because of in-stent restenosis of the LAD. Again three months later a TAXUS^{TM} stent (Boston Scientific) was implanted in the RCA because of subtotal in-stent restenosis extending into the recently implanted CYPHER^{TM} stent. Again, rapid progression of his CAD – now in the LCX – made a further intervention necessary (TAXUS^{TM} stent). Three months later the RCA was again subtotally restenosed; however the intermediate results in LAD and LCX were good (Fig. 2). Left ventricular function remained normal, the ejection fraction was calculated with 65%. Severe left ventricular hypertrophy was known for years because of a long history of arterial hypertonus. Hyperlipoproteinemia as an additional cardiovascular risk factor was treated with fluvastatin. Further medication included aspirin, clopidogrel, beta blocker, AT I receptor antagonist, and an antidepressant (doxepine) for endogenous depression.

After conventional PTCA of the RCA to open the occluded artery, local paclitaxel therapy was performed using the newly designed GENIE^{TM} application device (Globamed, Menzingen, Switzerland, s. Fig. 1). The intervention was primarily successful without measurable local or systemic side effects. Repeat angiography 3 and 9 months after intervention showed a patent RCA without restenosis. From the time of the intervention the patient remained free of cardiac events and symptoms for almost one year now (Fig. 3).

Discussion

In-stent restenosis of a previously stented coronary artery is a disease that is difficult to treat. Besides coronary artery bypass surgery with its specific

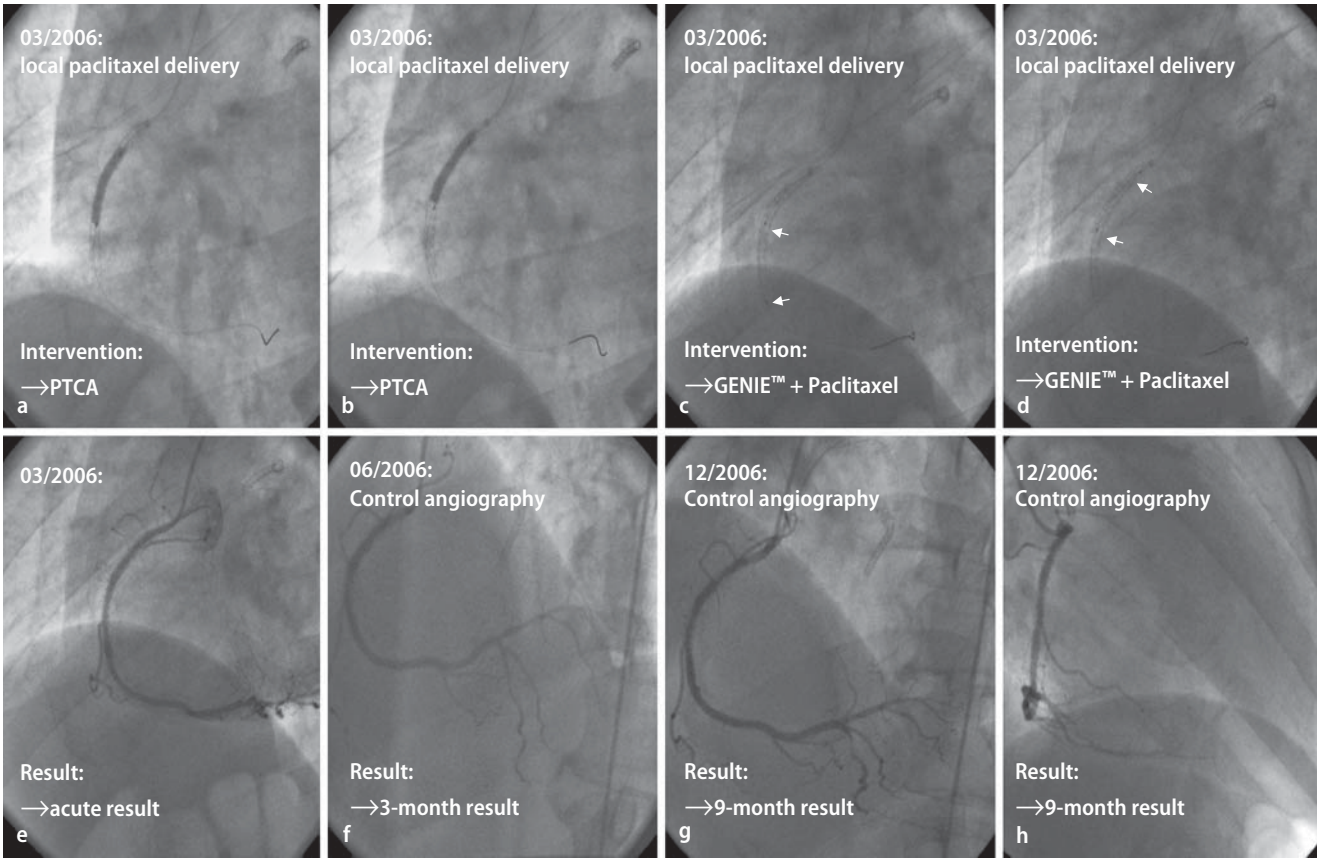

Fig. 3 Angiographic findings of the interventional procedure during local drug delivery and its results. After PTCA of in-stent restenosis (**a**, **b**), the GENIE catheter was placed (**c**, **d**) and inflated with low pressures of 2 atm for 60 s, resulting in a local delivery of 15 ml 10 μM paclitaxel covering all previously implanted stents even beyond the stent margins. Pictures **e**, **f**, **g**, **h** show the angiographic results of control angiography up to 9 months after intervention

problems and contraindications, repeat PTCA has shown to be hampered with poor results. A second implantation of a bare metal stent is not a promising option since it already has failed, which led to the increasing use of drug-eluting stents as common treatment option [1–3]. However this means not only the repeated implantation of a metal device in the same coronary lesion but also an off-label strategy that is currently increasingly disputed after recent unfavorable data for the drug eluting stent [1, 4]. In this patient, BMS and two different DES failed to prevent restenosis. The patient was then admitted to our institution and scheduled for CABG surgery. However, since his subtotally restenosed RCA was currently the only lesion that needed treatment, it was discussed with the patient to perform a catheter-based local delivery of paclitaxel via the GENIE^{TM} application device as a last percutaneous attempt before CABG surgery. The protocol for local intracoronary paclitaxel delivery was approved by our local ethics committee and the German Federal Institute for Drugs and Medical Devices. Written consent was obtained according to these formalities.

Catheter-based local antiproliferative therapy offers the advantage of a homogenous drug delivery of the whole intervention area even beyond stent struts without the disadvantages of a second stent and its coating material [5]. The GENIE^{TM} catheter consists of a percutaneous balloon having a distal and proximal segment with occlusive function and a central segment that allows for homogenous transfer of paclitaxel to the vessel wall. Three holes in the distal ramp fill the drug depot without additional trauma or hydrojets (s. Fig. 1). After conventional balloon dilatation and removal of the PTCA balloon, the catheter for local paclitaxel delivery is advanced over the wire and inflated at a low pressure of 2 atm that allows for distal and proximal occlusion of the vessel without additional trauma, while simultaneously forming a central drug depot. TAXOL^{TM} is sterile filtered, diluted in 0.9% saline and prepared for application in a final concentration of 10 μM. In this

case, three repeated inflations of 60 s each allowed for application of 15 ml TAXOL solution in Seg. 1 and 2 of the RCA covering all previously implanted stents (BMS, CYPHER and TAXUS). The lipophilic character of paclitaxel allows for rapid intracellular uptake using a non-traumatic application catheter. We could show that even short time incubation leads to long-lasting biological effects in vascular smooth muscle cells because of an irreversible alteration of the cytoskeleton, questioning the need for a sustained release of the drug from a stent polymer [6, 7]. Local catheter-based delivery of paclitaxel proved effective in different preclinical models [6, 8, 9]. In the pig coronary stent model, paclitaxel treatment via the GENIE^{TM} catheter led to a significant reduction of neointimal proliferation. All coronary arteries showed complete endothelialization 42 days following treatment [5]. Recent clinical data with a similar strategy (paclitaxel-coated balloon) are promising and suggest excellent efficacy in the treatment of in-stent stenosis [10]. The potential of a local paclitaxel treatment via the GENIE^{TM} catheter for preventing in-stent restenosis in *de novo* lesions is currently being evaluated in a randomized, prospective clinical trial in more than 200 patients (LOCAL TAX study, EudraCT-Nr: 2005-001481-14, clinicalTrials.gov identifier: NCT 00396929). Patient inclusion was completed in February of this year, and final data are expected at the end of 2007.

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