PCI of complex coronary lesions, new stent technologies, and clinical outcomes
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Significant intimal hyperplasia regression between 6 and 18 months following Genous™ endothelial progenitor cell capturing stent placement

Margo Klomp, Marcel AM Beijk, Jan GP Tijssen and Robbert J de Winter

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Introduction

While percutaneous coronary intervention (PCI) with stent implantation provides a safe and effective treatment for patients with symptomatic coronary artery lesions, neointimal hyperplasia resulting in in-stent restenosis continues to be a concern. After drug-eluting stent (DES) implantation, cytotoxic and cytostatic drugs inhibit smooth muscle cell proliferation to prevent intimal hyperplasia but at the same time hamper the endothelialization process crucial for vascular healing. In addition, after DES implantation continued accumulation of intimal tissue within the stent may continue well beyond the first 9-12 months after stent placement. After bare metal stenting, a natural biphasic pattern is seen with intimal tissue growth and luminal loss up to 6 months followed by a tissue volume regression and luminal gain between 6 months and 3 years. This similar biphasic pattern was observed in a study by Duckers et al. evaluating the bio-engineered Genous™ endothelial progenitor cell (EPC) capturing stent (ECS). The ECS is coated with immobilized CD34+ antibodies designed to capture circulating EPCs that subsequently form a new confluent endothelial layer covering the stent struts. In the study by Duckers et al. delayed luminal modification resulted in a late luminal loss reduction of 24.4% between 6- and 18-month follow-up. Considering the outcome of this study, repeat revascularization of angiographically moderate restenosis may best be avoided in patients without anginal complaints or ECG changes in the first year after ECS implantation. In our study we aim to provide a detailed per-patient overview of intimal hyperplasia regression between 6- and 18-month follow-up in ECS-treated patients.

Materials and methods

Source population

The data analyzed in our study were obtained from all patients in our center treated with the ECS and with complete 6- and 18-month angiographic follow-up.

Our institution is a high-volume, tertiary referral hospital with on-site cardiac surgery. All interventions were performed according to standard PCI guidelines. At the start of the procedure, all patients received 5000 IU of unfractionated heparin. The use of peri-procedural glycoprotein IIb/IIIa receptor inhibitors was left at the discretion of the operator. After the PCI, patients were treated with aspirin 100 mg indefinitely and clopidogrel 75 mg daily for one month.

Data source

Clinical baseline and procedural information for all performed procedures were retrieved from our electronic PCI database. When a major cardiac event was reported, review of hospital records, chart review, telephone contact with the referring cardiologists and/or the patient’s general practitioner were used to complete the information.
Endothelial progenitor cell capturing stent

The Genous Bio-engineered R stent™ (OrbusNeich Medical Technologies, Fort Lauderdale, FL, USA) is a 316L stainless steel stent coated with monoclonal murine anti-human CD34+ antibodies on the adluminal surface. These anti-CD34+ antibodies specifically target the circulating EPC population associated with neovascularization and arterial repair response. Attraction of EPCs may lead to rapid endothelialization and thereby may lead to improved clinical outcomes.

Coronary angiography and Quantitative Coronary Analysis (QCA)

Coronary angiograms were obtained at 4 different time points: 1) before the PCI procedure, 2) directly after stent placement, 3) at 6-month follow-up, and 4) at 18-month follow-up. Complete angiographic dataset was available from 14 patients.

For adequate endpoint assessment, follow-up angiographic views were recorded using the same planes as used at baseline procedure. All angiograms were performed under routine protocol by experienced operators and were recorded in such a way that they were suitable for off-line QCA. Standard off-line QCA was performed by the AMC core lab using the QCA-CMS® 6.0 system of Medis medical imaging systems B.V., Leiden, the Netherlands. Binary angiographic restenosis was defined as diameter stenosis (DS) of >50% at follow-up angiography. Late loss was defined as the difference between the minimal luminal diameter (MLD) after stenting and the MLD at follow-up.

Statistical analysis

Our study was designed as an exploratory, retrospective study. Continuous various variables were summarized by mean±standard deviation. Post-procedural and 6-month and 18-month follow-up angiographic changes were compared using a 2-tailed, paired samples t-test. P<0.05 was considered to be statistically significant.

Results

Baseline and procedural characteristics

The average age of our study population was 59 years, 57% were male and 14% were diabetics. Table 1 provides a detailed overview of the baseline characteristics. A total of 17 lesions were treated of which 16 were suitable for QCA analysis and 94% of the lesions analyzed at baseline were type A/B1 lesions. Mean lesion length was 14.1±4.7mm, mean stent length was 17.2±5.7mm and mean vessel diameter was 3.3±0.4mm with 1.2±0.4 stents per patient used. (Table 2)
Follow-up

Mean 6-month angiographic follow-up was performed at 180 days and mean 18-month follow-up at 562 days. One patient underwent a clinically-driven target lesion revascularization at 540 days and angiographic data retrieved from this procedure were used for our 18-month analysis. There were no deaths, no myocardial infarctions or stent thrombosis (ST), or bypass surgery during the 18 months of follow-up. (Table 3)

All patients received aspirin indefinitely and were prescribed clopidogrel for 1 month. One patient discontinued clopidogrel after 1 day, 6 after 1 month, 1 after 6 months, 5 after 12 months and 1 was still on dual anti-platelet therapy after 18 months.
Figure 1 The course of the mean luminal diameter per treated lesion at 4 the different time-points; pre-procedural, post-procedural, at 6-month follow-up and 18-month follow-up.

Table 2. Baseline angiographic and procedural characteristics

<table>
<thead>
<tr>
<th></th>
<th>n = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target coronary artery</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Right</td>
<td>7 (44%)</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>ACC/AHA lesion classification</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>7 (44%)</td>
</tr>
<tr>
<td>B1</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>B2</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>C</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>14,1 ± 4,7</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>17,2 ± 5,7</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3,3 ± 0,4</td>
</tr>
<tr>
<td>Stents per lesion</td>
<td>1,2 ± 0,4</td>
</tr>
</tbody>
</table>

values are n (%) or mean±SD
Angiographic outcome
At 6-month follow-up, the average MLD was 1.89±0.60mm compared to 2.71±0.39mm post-procedure, and the in-stent late loss was 0.82±0.44mm by means of QCA. (Table 4) The percentage volume obstruction was 38.86±15.02 with a binary restenosis rate of 31.3%. At 18-month follow-up, we observed a significant regression of intimal hyperplasia with a MLD of 2.17±0.54mm and a late loss of 0.54±0.44mm, indicating a decrease in late loss of -34.1%. (Correlation coefficient: 0.759; p=0.001) The percentage volume obstruction

<table>
<thead>
<tr>
<th>Table 3. QCA analysis per lesion</th>
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<tr>
<td>Post procedure</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Angiographic success</td>
</tr>
<tr>
<td>Procedure success</td>
</tr>
<tr>
<td>RVD (mm)</td>
</tr>
<tr>
<td>MLD (mm)</td>
</tr>
<tr>
<td>Volume obstruction (%)</td>
</tr>
</tbody>
</table>

*values are n (%) or mean±SD. RVD reference vessel diameter, MLD mean luminal diameter. *paired sample T-test. **paired sample correlation

Figure 2 Angiographic frames on all 4 time points of 3 patients with significant intimal hyperplasia regression between 6 and 18 months.
was 29.25±12.67 (a decrease of 24.7%) and the binary restenosis rate was 25% lower; 6.3%.

Figure 2 shows the angiographic images on all 4 time points of the 3 patients with most outspoken intimal hyperplasia regression between 6 and 18 months.

Discussion

Our study clearly demonstrates that in coronary artery vessels treated with the ECS significant intimal hyperplasia regression occurs between 6- and 18-month follow-up. While the exact mechanism of this phenomenon in the ECS has not been investigated on a pathological level, one may hypothesize that its healing mechanism parallels that of the bare metal stent rather than the drug-eluting stent. DES release cytotoxic or cytostatic medication inhibiting both smooth muscle cell proliferation and neo-endothelialization of the stent struts. Although DES implantation frequently results in a desirable minimal late loss when evaluating a follow-up angiogram at 6-9 months, several studies demonstrated a continuing increase of neointimal volume after the first year of DES implantation. The study by Morice et al. shows the 1-, 3-, and 5-year rates of freedom from target lesion revascularization (TLR) when comparing the sirolimus-eluting stent (SES) with the bare-metal stent (BMS). In the SES population, the rates were 99.2%, 93.8%, and 89.7%, and in the control group 75.9%, 75.0%, and 74.0% respectively. (p < 0.001; log-rank). While the SES shows a lower overall TLR rate, an ongoing, higher increase in TLR is observed between the first and fifth year of 9.5% whereas only a 1.9% increase in the control group. One may conclude that the risk of TLR after the first year of stent implantation is therefore higher in patients treated with a SES than with a BMS. Furthermore, the delayed functional endothelialization of the stent struts prevents the natural healing response and may thereby be associated with vasomotor dysfunction and the occurrence of very late stent related thrombosis.

In contrast, the healing process after BMS implantation in humans follows the more natural course of physiological wound healing. Directly after BMS implantation, multilayered thrombus will cover the damaged area followed by a granulation tissue response with smooth muscle cell (SMC) migration and proliferation together with inflammatory cell infiltration resulting in neovascularization and re-endothelialization. After 2-4 weeks, the acute inflammation subsides and is replaced by chronic inflammatory cells; the thrombus started organizing and a thin provisional extracellular matrix (ECM) is formed. Beyond 1 month, the chronic inflammation persists and ECM and SMCs further enrich the expanding neointima. Importantly, beyond 18 months of implantation, the neointima of the stented area becomes richer in type I collagen and less cellular (potentially via SMC apoptosis) causing the observed negative remodelling in the BMS.

Animal studies testing the ECS have shown that, only after 48 hours of implantation, the stent struts are covered with a confluent endothelial monolayer and these endothelial cells exhibit a cobblestone-like phenotype, indicative of a mature functional endothelium. At 28 days follow-up, the ECS-stented area showed a mature neointima with an average
inflammatory score similar to the control BMS and a significant reduction in neointimal area was seen in the ECS when compared to the BMS.\textsuperscript{16} In the current analysis, late luminal loss was 0.82±0.44mm at 6-month follow-up showing that rapid endothelialization after ECS implantation did not cause the desired intimal tissue reduction similar to a DES.\textsuperscript{17,18} In contrast however, at 18-month follow-up, statistically significant intimal hyperplasia reduction was demonstrated in ECS-treated patients. Based on the results of the current analysis and the ongoing intimal hyperplasia observed in the DES, we hypothesized that to fairly compare late loss numbers of the ECS to the DES, study-related angiographic follow-up should be performed after 18 months or even hereafter.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.\textsuperscript{19}
References


