Endothelial progenitor cell capture stents - practical use of cell mobilisation.
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The use of endothelial progenitor cells capture stents (EPC-capture stents) may be particularly beneficial in patients with a high risk of thrombosis (diabetes, stenting of small vessels and long lesions), in whom, due to contraindications - gastrointestinal bleeding, active peptic ulcer disease, non-compliance or a need for surgical procedures - dual antiplatelet therapy for the prolonged period cannot be maintained.

Background

The short and long-term efficiency of PCI is limited to in-stent restenosis (ISR) and thrombosis.

Expansion of the stent in the target artery induces local injury of the vessel wall, primarily from the disruption of the endothelial lining. Following the injury, the reparatory mechanisms are activated leading to recovery of the endothelial coverage over the stent struts.

Disruption of the endothelium causes the activation and adherence of platelets (minutes-hours) and recruitment of the monocytes and leukocytes (hours to days). The time that elapses between the endothelial disruption caused by the expanded stent and full coverage of the struts with new endothelial cells carries the highest risk of in-stent thrombosis. During this same time frame, the initial events of ISR occur, - primarily migration and proliferation of smooth muscle cells (1,2). The key event in rebuilding the endothelial layer over the stent struts is the recruitment of circulating endothelial progenitor cells (EPC), their adherence and attachment to the surface of the stent and vascular wall between the struts. The full coverage of the prothrombotic metal struts with new endothelial cells reduces the initially high risk of thrombosis. The repair processes are completed after 1 month when bare metal stents are used, and over 6 months after DES implantation.

The course of events is different after implantation of drug-eluting stents (DES). Recruitment of the inflammatory cells as well as smooth muscle cells is reduced and slowed. This effect is associated with a reduced potential for neointima formation (ISR), but also with an unfavorable lag in reendothelialisation.

As shown in studies using angioscopy, thrombus formation over the DES struts can be seen as long as 6 months after PCI. The effect is probably caused by the inhibitory effects of immunosuppressive, antimitotic and antiinflammatory drug released from the stent on the EPCs adhering to the place of vascular injury and the struts (1-3).

The use of DES significantly reduced the risk of ISR, but the slowing and prolongation of the reparatory process may increase the risk of the late in-stent thrombosis as well as other unwanted effects, such as edge effect and formation of the coronary aneurysms.

- The risk of late thrombotic effects of DES is mainly associated with discontinuation of dual antiplatelet therapy, therefore the treatment should be continued for at least 12 months or even indefinitely. The following groups
of patients have a particularly high risk of in-stent thrombosis:

- Acute coronary syndromes
- Cardiogenic shock
- Diabetes
- Procedure-related parameters (coronary dissection, long lesion, small vessel diameter, use of multiple stents)

On the other hand, prolonged dual anti-platelet therapy is associated with significant risk (bleeding, thrombocytopenia) especially in patients with peptic ulcer disease and in the elderly. Discontinuation of this therapy is also indicated in patients undergoing surgery, which may increase the risk of thrombotic events (1).

The concept of EPC-capture stents

Numerous studies have shown that circulating EPCs contribute to the repair of the endothelium after injury, most likely by repopulating the site of stent implantation.

The number of circulating EPCs is considered a marker of the turnover of the endothelium, as well as a promising marker of the cardiovascular risk.

EPCs can be identified by the presence of surface markers - CD34, CD133 - or vascular endothelial growth factor type 2 receptor (VEGFR2) which can be identified using labeled monoclonal antibodies.

Since EPCs represent a pool of cells which contribute to the endothelial repair after vascular injury, the increased homing and retention of these cells at the site of stent implantation may increase and speed up the process of endothelialisation.

Introduction of a bioengineered stent with the immobilised antibody against CD34 antigen bound to the surface of the struts represents significant progress in the prevention of thrombotic events. The surface of the BMS is primed to obtain biocompatible matrix and the murine monoclonal antibody against human epitopes of CD34 are attached by covalent binding (4-6).

Animal Models

Animal studies revealed that the number of EPCs attaching to the stent struts is significantly higher after 1 and 48 hours post implantation and at 48 hours, more than 70% of the surface of stent struts is covered with endothelial cells. The cells are spindle shaped and aligned with the direction of blood flow forming the confluent monolayer dispersed over the stent struts and between them.

There is also a trend towards lesser intensity of the neointimal formation and stenosis areas in comparison to the BMS after 28 days. More than 80% of cells captured by the monoclonal antibody express the markers of endothelial cells, while only 30% of the cells are positive for EC markers on the surface of BMS. The complete endothelial coverage was observed just 48 hours after using the EPC-capture stents and a significant degree of endothelialisation was present within 1 hour after implantation (7,8).

Clinical Trials

EPC-capture stents received the CE mark and are commercially available since 2005. So far, the results of two studies carried out in patients with stable CAD were published.

First in-man study (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth, HEALING-FIM) demonstrated the safety and feasibility of the use of EPC-capture stents (Genous, OrbusNeich) in 16 patients with stable CAD with 100% procedural success and 6.3% rate of MACE in 9-month follow-up (9).

The multicenter HEALING II study included 63 patients with stable CAD, 67% had hyperlipidemia, 16% diabetes, 24% a history of myocardial infarction and 52% a positive family history of CAD. Patients with either de novo or non-stented restenotic primarily type B2 and C lesions in target native coronary vessels with a diameter of 2.5-3.5 and a 9.83 mm average length were enrolled.

At 6 and 9-months follow-up, the clinically driven target lesion revascularisation (TLR) rate was 6.3% and the MACE rate was 7.9%. The binary restenosis was 0% and late loss 0.48 mm. There were no additional events at additional 18-months follow-up. The dual antiplatelet therapy was maintained for 1 month and no thrombotic events were recorded. Importantly, in angiographic control, the late loss regressed by 18% between 6 and 18 months of follow-up (10,11).
Further important data will be available when the HEALING IIB (ClinicalTrials.gov Identifier: NCT00349895) multicenter study with control angiography after 6 and 18 months is completed. This study will further clarify the role of combined therapy with statins and implantation of EPC capture stents. All 90 patients receive 80mg of atorvastatin at least 2 weeks prior to the procedure in order to achieve EPC mobilisation (12).

In addition, the manufacturer launched an eHEALING real-life registry which aims to analyse the outcomes in more than 5000 patients after EPC-capture stents implantation. So far over 2500 patients were included in the eHEALING registry (13).

**Statins and EPC-capture stents**

Importantly, the number of circulating EPCs positively correlates with a favorable clinical outcome. Only patients with a low number of EPC sustained MACE and ISR at 6 months follow-up, which shows that the endogenous capacity to mobilise the EPC is very important in vascular healing after stent implantation.

HEALING II patients on statins had an approximately twofold increase in the EPC number when compared to patients without statins. The safe and efficient way to mobilise cells is statin therapy which does not only significantly increase the number of EPC, but also improves their functional capacity. This is a particularly important issue in patients with diabetes and in the elderly, where the number of EPCs is significantly lower in comparison to younger and non-diabetic subjects. Also, the functional capacity of the EPCs is impaired in patients with diabetes and multiple CVD risk factors (12-14).

**Summary**

To conclude, the use of EPC-capture stents may be particularly beneficial in patients with a high risk of thrombosis (diabetes, stenting of small vessels and long lesions), in whom, due to contraindications (gastrointestinal bleeding, active peptic ulcer disease), non-compliance or the need for surgical procedures, dual antiplatelet therapy for the prolonged period cannot be maintained.

The use of EPC-capture stents was investigated in stable coronary heart disease, and proved effective and safe. It has to be tested in other patient populations such as acute coronary syndromes. If proven safe and effective, this approach can reduce restenosis to the levels comparable with DES, without the risk of late thrombosis inherent to DES, and without the risk of long-term dual antiplatelet therapy.

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