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ABSTRACT

Objective: The effects of stem cell therapy on the coronary vasculature were investigated in patients with acute myocardial infarction who underwent peripheral blood stem cell (PBSC) therapy in the MAGIC Cell-3-DES study.

Methods: Among 50 patients with acute myocardial infarction who underwent either sirolimus-eluting stent or paclitaxel-eluting stent implantation for the culprit lesion, intravascular ultrasound was analysed in 36 patients (cell infusion: n = 19 and control: n = 17). In the cell infusion group, PBSCs mobilised by granulocyte-colony stimulating factor were delivered via intracoronary infusion into infarcted myocardium. Proximal and distal reference segments, and stented segments, were evaluated with intravascular ultrasound at immediate post-intervention and 6-month follow-up, respectively.

Results: In the proximal and distal reference segments, the serial changes of lumen area, vessel area, and plaque plus media area were not significantly different between the cell infusion and the control groups. Within stented segments, mean neointimal area was similar in the two groups (cell infusion: 0.2 (SD 0.5) mm^2 vs control: 0.3 (SD 0.4) mm^2, $p>0.05$). However, there was a significant increase in mean peri-stent area of stented segment in the cell infusion group compared with the control group (0.7 (SD 1.4) mm^2 vs −0.1 (SD 1.2) mm^2, $p<0.05$). This difference mainly came from paclitaxel-eluting stent-implanted patients.

Conclusion: Intracoronary infusion of PBSCs mobilised with G-CSF does not aggravate de novo atherosclerotic lesion and neointimal hyperplasia with DES implantation. However, it may induce peri-stent tissue growth at the stented segment, especially in patients receiving PES. Its clinical significance needs to be evaluated with long-term follow-up.

Recent clinical trials have shown favourable effects of bone marrow-derived stem cell therapy on left ventricular function and remodelling after myocardial infarction.[1–4] However, the possibility that stem cell therapy might aggravate de novo atherosclerosis or restenosis has also been suggested and regarded as a potential limitation of stem cell therapy.[3–6] Recently, we reported the results of the Myocardial Regeneration and Angiogenesis in Myocardial Infarction with G-CSF and Intracoronary Stem Cell Infusion-3-Drug eluting stent trial (MAGIC Cell-3-DES trial), which showed a favourable effect of intracoronary infusion of peripheral blood stem cells (PBSCs) mobilised by granulocyte colony-stimulating factor (G-CSF) with drug-eluting stent (DES) implantation on left ventricular systolic function and remodelling in patients with acute myocardial infarction (AMI) without any risk for restenosis based on angiographic data.[7] However, the effects of intracoronary infusion of stem cells on the coronary vasculature, including neointimal growth and vascular remodelling within stented segments or de novo atherosclerotic lesions, are mostly unknown. The aim of this study was to evaluate the effect of infusion of PBSCs mobilised by G-CSF on segments stented with DES and segments without intervention using serial quantitative intravascular ultrasound (IVUS) analyses.

METHODS

Patient selection

The MAGIC Cell-3-DES trial was a randomised, controlled trial to recruit 50 patients with acute and 36 patients with old myocardial infarction, respectively. In this study, AMI was defined as randomisation within 14 days from onset of new ST-segment elevation myocardial infarction. Eligible for enrolment were patients who were successfully revascularised at the culprit lesion with the use of either sirolimus-eluting stents (SES; Cypher, Cordis, Miami Lakes, FL) or paclitaxel-eluting stents (PES; TAXUS, Boston Scientific Corporation, Boston, MA). The current IVUS study included only patients with AMI who underwent serial IVUS examination at post-intervention and 6-month follow-up and whose IVUS data were adequate for analysis. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital. Informed written consent was obtained from all patients after the procedure and risk of the study had been explained.

Stem cell mobilisation, characterisation and intracoronary infusion

In the cell infusion groups after successful stent implantation, PBSCs were mobilised from bone marrow by G-CSF (Dong-A Pharmaceutical, Seoul, Korea) at 10 μg/kg body weight for 3 days. On day 4, mobilised PBSCs were collected with COBE spectra apheresis system (COBE BCT Inc., Lakewood, CO, USA) using the mononuclear cell collection method. The infusion cell doses were 1–2×10^9 mononuclear cells per patient to guarantee the minimum target cell dose of 7×10^6 CD34+ cells. We infused PBSCs selectively into infarcted

myocardium via over-the-wire balloon catheter as previously described.[3] Placebo was not applied to the control group.

Quantitative angiographic analysis

Coronary angiograms were obtained at baseline and 6-month follow-up. Quantitative coronary angiographic analysis (QCA) was performed by an independent blinded specialist with Quantcor QCA V4.0 program (Pie medical imaging, The Netherlands).

Intravascular ultrasound imaging

Serial IVUS examinations at post-intervention and 6-month follow-up were performed in an identical fashion using a commercially available system (ClearView or Galaxy2, Boston Scientific Corporation, USA). Before insertion of the IVUS catheter, nitroglycerin 100–200 μg was injected into the coronary artery. The catheter was advanced at least 10 mm beyond the stented segment, and imaging was performed from there to the aorto-ostial junction. The transducer was withdrawn automatically at a speed of 0.5 mm/s. All IVUS images were recorded on VHS videotape and digitalised for off-line analysis.

Intravascular ultrasound analysis

IVUS images were analysed by a single experienced operator, blinded to patients' information, using the EchoPlaque 2.7 (INDEC Systems Inc., Mountain View, CA). The leading edges of the lumen, stent and external elastic membrane (EEM) borders were traced by manual planimetry. We performed quantitative analysis in the stented segment and the proximal and distal reference segments, which were defined as 5-mm vessel segments proximal and distal to the stents. If the EEM could not be detected due to heavy calcification with acoustic shadowing or side branches located within the 5-mm segment proximal or distal to the stent, that segment was excluded from analysis. Cross-sectional area of the lumen, the stent, and EEM were measured in steps of 1 mm, and mean values of each parameter in each segment were regarded as mean lumen area (LA), mean stent area (SA), and mean vessel area (VA), respectively. Mean plaque plus media area (PMA) in the proximal and distal reference segments was derived by VA − LA, and mean neointimal area (NIA) and mean peri-stent area (PSA) in the stented segment were derived by SA − LA and VA − SA, respectively.

Statistical analysis

Categorical variables are given as percentages and were tested with Fisher's exact test. Continuous variables are presented as mean (SD). Area changes (Δ values) for each measurement were calculated as follow-up minus post-intervention value. Comparisons between post-intervention and 6-month follow-up values were performed using the Wilcoxon signed rank test, whereas comparison between two groups was performed using the Mann–Whitney U test. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using the SPSS program (version 12.0, SPSS Inc., Chicago, IL).

RESULTS

Study population and baseline characteristics

In the MAGIC Cell-3-DES trial, 50 patients with AMI completed 6-month follow-up. Among these patients, we completed evaluation in 36 patients who had analysable post-intervention baseline and 6-month follow-up IVUS data for the present study (control: n = 17, cell infusion: n = 19). Serial IVUS was available for the stented segment in 17 control and 19 cell infusion patients, for the proximal reference segment in nine control and 14 cell infusion patients, and for the distal reference segment in 14 control and 16 cell infusion patients, respectively. In the proximal reference segments, 13 segments were not analysable due to ostial lesion (n = 8), heavy calcification (n = 2) or presence of side branches (n = 3). In the distal reference segments, six segments were not analysable due to heavy calcification (n = 2) or presence of side branches (n = 4). Only two patients in the control group experienced angiographic binary restenosis at 6-month follow-up, and one patient was included in the IVUS study.

The baseline characteristics of the patients and pharmacological treatment during the follow-up period are shown in table 1. There were no significant differences in the baseline characteristics between the two groups except for the low density lipoprotein cholesterol (LDL) level. The baseline procedural parameters and quantitative angiographic data are summarised in table 1. Procedural parameters were similar in the two groups. As measured by QCA, there were no significant differences in

Table 1 Baseline characteristics of patients

	Control	Cell infusion	p Value
Clinical and laboratory data			
No. of patients	17	19	
Age (years)	56.0 (13.4)	57.0 (13.5)	0.83
Male	14 (82%)	16 (84%)	1.00
Current smoker	8 (47%)	9 (47%)	1.00
Diabetes mellitus	4 (24%)	4 (21%)	1.00
Hypertension	6 (35%)	9 (47%)	0.52
Hypercholesterolaemia	5 (29%)	3 (16%)	0.43
Medication			
Aspirin	17 (100%)	19 (100%)	1.00
Clopidogrel	17 (100%)	19 (100%)	1.00
ACE inhibitor/AT-II receptor blocker	16 (94%)	19 (100%)	0.47
β-blocker	14 (82%)	17 (89%)	0.65
Statin	14 (82%)	14 (74%)	0.70
Lipid profiles			
Total cholesterol	179.8 (21.4)	195.1 (28.4)	0.10
Low density lipoprotein cholesterol	108.6 (25.6)	129.3 (24.0)	<0.05
High density lipoprotein cholesterol	43.8 (11.5)	39.3 (9.6)	0.26
Triglyceride	98.3 (38.8)	127.4 (51.3)	0.09
hs-CRP	4.90 (5.71)	4.29 (4.31)	0.76
Procedural and quantitative angiographic data			
Target vessels			
LAD/LCX/RCA	6/3/8	11/1/7	0.28
Balloon-to-artery ratio	1.21 (0.32)	1.12 (0.15)	0.43
Maximal inflation pressure, atm	13.1 (2.1)	13.9 (2.5)	0.32
Stent size, mm	3.13 (0.33)	3.05 (0.30)	0.38
Stent length, mm	31.8 (14.3)	29.3 (9.8)	0.54
Quantitative angiographic data			
Proximal reference vessel diameter, mm	3.20 (0.33)	3.20 (0.40)	0.96
Minimal luminal diameter, mm			
Post-intervention	2.95 (0.38)	2.83 (0.47)	0.42
6-month follow-up	2.64 (0.56)	2.61 (0.56)	0.85
Late luminal loss, mm	0.30 (0.41)	0.23 (0.22)	0.47

Results expressed as mean (SD) unless otherwise stated.
hs-CRP, high sensitivity C-reactive protein; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

reference vessel diameter and minimal luminal diameter at post-intervention.

Clinical and angiographic variables at 6-month follow-up

Target vessel revascularisation was performed in one control patient, and no other major adverse cardiovascular events were noted during follow-up. At 6-month follow-up, hs-CRP and LDL cholesterol levels significantly decreased in both groups (% change in hs-CRP −65.6% vs −95.1%; % change in LDL cholesterol −33.5% vs −27.9% for control vs cell infusion group, respectively, $p<0.05$). As for angiographic variables at follow-up, late luminal loss was similarly low in both groups (control 0.30 (SD 0.41) vs cell infusion 0.23 (SD 0.22) mm, $p = 0.47$) and thus the minimal luminal diameter was similar in the two groups (2.64 (SD 0.56) vs 2.61 (SD 0.56) mm, $p = 0.85$).

Changes of plaque areas within the proximal and distal reference segments

As shown in table 2, the mean lumen area, vessel area, and plaque plus media area of the proximal and distal 5-mm reference segments were similar in the control and cell infusion groups at immediate post-intervention and 6-month follow-up. The interval changes of mean LA, VA, and PMA during 6 months also showed no significant differences between the two groups.

Changes of plaque areas within the stented segments (fig 1)

Table 3 summarises the quantitative IVUS parameters within the stented segments. The neointimal area at 6 months was similar in the two groups (control 0.3 (SD 0.4) mm^2 vs cell infusion 0.2 (SD 0.5) mm^2, $p = 0.28$). The interval changes of mean lumen area during 6 months showed no significant difference, suggesting no aggravation of neointimal growth with intracoronary stem cell infusion. However, there was a significant increase in vessel area and peri-stent area of stented segment in the cell infusion group compared with the control group. When the patients were divided by the type of DES implanted (table 2), we found that the significant increase in the vessel area and peri-stent area in the cell infusion group was mainly due to the effects of cell infusion in those receiving PES.

Table 2 Intravascular ultrasound results of proximal and distal reference segments

	Control	Cell infusion	p Value
Proximal reference segment	n = 9	n = 14	
Post-intervention			
Mean lumen area, mm^2	7.9 (1.9)	7.7 (1.9)	0.69
Mean vessel area, mm^2	15.2 (5.3)	16.3 (3.1)	0.14
Mean plaque plus media area, mm^2	7.2 (3.9)	8.6 (2.2)	0.09
6-month follow-up			
Mean lumen area, mm^2	8.2 (1.8)	8.0 (1.8)	0.61
Mean vessel area, mm^2	15.7 (4.6)	16.3 (2.9)	0.44
Mean plaque plus media area, mm^2	7.5 (3.4)	8.4 (1.9)	0.18
Interval changes			
Δ Mean lumen area, mm^2	0.3 (0.8)	0.3 (1.1)	0.98
Δ Mean vessel area, mm^2	0.5 (1.9)	0.1 (2.0)	0.61
Δ Mean plaque plus media area, mm^2	0.2 (1.1)	−0.2 (1.5)	0.41
Distal reference segment	n = 14	n = 16	
Post-intervention			
Mean lumen area, mm^2	5.9 (2.5)	5.7 (1.8)	0.89
Mean vessel area, mm^2	10.7 (4.5)	10.7 (3.9)	0.98
Mean plaque plus media area, mm^2	4.8 (2.2)	5.0 (2.7)	0.98
6-month follow-up			
Mean lumen area, mm^2	5.8 (2.3)	5.9 (1.8)	0.55
Mean vessel area, mm^2	10.7 (4.3)	11.1 (4.0)	0.73
Mean plaque plus media area, mm^2	4.9 (2.4)	5.1 (2.7)	0.99
Interval changes			
Δ Mean lumen area, mm^2	−0.1 (0.5)	0.2 (0.8)	0.16
Δ Mean vessel area, mm^2	0.0 (0.5)	0.4 (1.1)	0.19
Δ Mean plaque plus media area, mm^2	0.1 (0.3)	0.1 (0.8)	0.60

Results expressed as mean (SD).

DISCUSSION

This study reports for the first time serial IVUS analysis after intracoronary infusion of PBSCs mobilised by G-CSF in patients with acute myocardial infarction treated by DES implantation. The major findings of this study are as follows: 1) cytokine-based stem cell therapy with intracoronary infusion of mobilised PBSCs did not aggravate in-stent neointimal hyperplasia in the case of DES implantation; 2) intracoronary infusion of PBSCs after cytokine therapy did not adversely affect de novo lesions in the proximal and distal segments of DES; 3) intracoronary stem cell infusion after cytokine therapy showed positive remodelling within the DES segment, especially in patients receiving PES.

Effect of intracoronary infusion of PBSCs on neointimal hyperplasia

In 2004, we reported that G-CSF was associated with greater late lumen loss and higher restenosis rates after bare metal stent implantation, especially when G-CSF was injected before stent implantation.[3] In another study, we showed that G-CSF-mediated neointimal growth was associated with mobilisation of smooth muscle progenitor cells and inflammation induced by G-CSF.[8] In this situation, DES was effective in preventing neointimal growth aggravated by G-CSF, while G-CSF facilitated re-endothelialisation of DES.[8] Based on these findings we conducted the MAGIC Cell-3-DES trial, in which we found that the combination of G-CSF-mobilised stem cell therapy with DES was safe and effective, and that infusion of the cells mobilised by G-CSF did not aggravate in-stent restenosis after DES implantation based on angiographic analysis.[7] In this IVUS substudy, there was no significant difference in mean area of neointimal hyperplasia analysed by IVUS between the control and the cell infusion group, confirming our previous angiographic findings that the risk of in-stent restenosis was not increased after cytokine-based peripheral blood stem cell therapy with DES implantation.

Effect of intracoronary infusion of PBSCs on de novo atherosclerotic lesions

Although conflicting data have been reported with regard to the effect of stem cell therapy on de novo atheromatous plaque progression, it has been persistently suggested that the possibility of progression of atherosclerosis after stem cell therapy might be a potential limitation. Several reports demonstrated that transplantation of bone marrow-derived mononuclear cells or spleen cell-derived endothelial progenitor cells induced progression of atherosclerotic plaque in apolipoprotein E knockout mice.[5 6] In contrast, atheroprotective effects of bone marrow-derived progenitor cells were proposed by Rauscher *et al*.[9] Replenishment of endothelial cells would result in restoration of attenuated endothelial cell function and protective effects against atherosclerosis. Adding to these conflicting results in experimental models, there are few data elucidating changes of de novo atherosclerotic lesions after stem

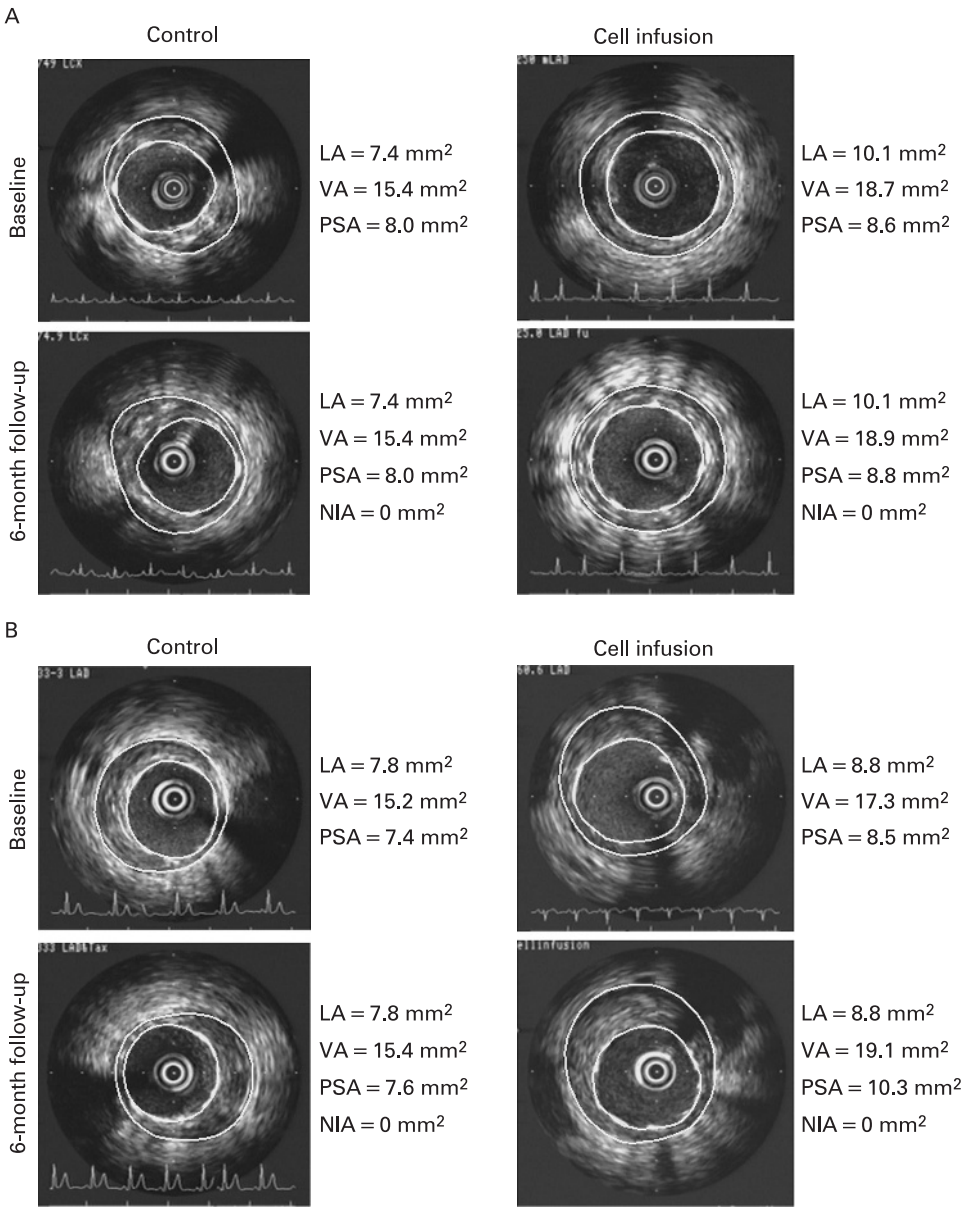

Figure 1 Exemplary cases of patients who received sirolimus-eluting (A) and paclitaxel-eluting stents (B). Cell infusion does not aggravate neointimal growth compared with baseline. However, the patient who was given a paclitaxel-eluting stent showed positive peri-stent remodelling at 6-month follow-up.

cell therapy, and these were mainly derived from clinical trials using bone marrow-derived stem cells. Cytokine-based PBSC therapy would be different from bone marrow-derived stem cell therapy, because the former has a tendency to increase systemic inflammation, which may be a determining factor for progression of atherosclerosis as well as neointimal growth. Therefore, we evaluated the serial changes of de novo atherosclerotic lesions in reference segments after intracoronary infusion of PBSCs after cytokine therapy by quantitative IVUS analysis to assess the effect of G-CSF-based stem cell therapy on de novo atherosclerotic lesions. Our results showed no significant differences between the control and the cell infusion group in the serial changes of mean lumen area, vessel area and plaque plus media area. To the best of our knowledge, this is the first report on the effect of intracoronary stem cell therapy on the change in human coronary de novo atherosclerosis using IVUS. Our results also support the safety of G-CSF-based stem cell therapy, showing that, at least, it does not aggravate de novo atherosclerosis.

Effect of intracoronary infusion of PBSCs on peri-stent remodelling of stented coronary artery

An interesting finding from this study was that peri-stent positive remodelling was observed without significant change in lumen area at 6-month follow-up after intracoronary PBSC infusion with DES implantation in patients with AMI, whereas there was no significant interval change in the control group. This result was mainly due to the effect of PBSC infusion in patients implanted with PES rather than SES, suggesting a different biological effect of intracoronary stem cell infusion depending on the type of drug released from the stent.

There are several issues to be investigated to explain this novel finding. The first issue is the reason why stem cell therapy preferentially induced peri-stent tissue growth in stented segments. Tanaka *et al*[10] reported that bone marrow cells were preferentially involved in the progression of neointimal hyperplasia only with injury causing endothelial denudation. Therefore, infused stem cells would mainly contribute to tissue growth in the segment subjected to severe injury causing

Table 3 Intravascular ultrasound results of stented segment

	Control	Cell infusion	p Value
Total segments	n = 17	n = 19	
Post-intervention			
Mean lumen area, mm²	6.5 (1.7)	6.6 (1.4)	0.71
Mean stent area, mm²	6.5 (1.7)	6.6 (1.4)	0.71
Mean vessel area, mm²	14.9 (3.4)	14.8 (2.7)	0.96
Mean peri-stent area, mm²	8.4 (2.2)	8.2 (1.9)	0.82
6-month follow-up			
Mean lumen area, mm²	6.2 (1.8)	6.4 (1.4)	0.60
Mean stent area, mm²	6.5 (1.7)	6.6 (1.3)	0.68
Mean vessel area, mm²	14.8 (3.0)	15.5 (3.1)	0.55
Mean neointimal area, mm²	0.3 (0.4)	0.2 (0.5)	0.28
Mean peri-stent area, mm²	8.3 (1.8)	8.9 (2.2)	0.63
Interval changes			
Δ Mean lumen area, mm²	−0.3 (0.4)	−0.2 (0.5)	0.19
Δ Mean stent area, mm²	0.0 (0.0)	0.0 (0.1)	0.26
Δ Mean vessel area, mm²	−0.1 (1.2)	0.7 (1.4)	0.042
Δ Mean neointimal area, mm²	0.3 (0.4)	0.2 (0.5)	0.28
Δ Mean peri-stent area, mm²	−0.1 (1.2)	0.7 (1.4)	0.05
SES-implanted segments	n = 10	n = 13	
Post-intervention			
Mean lumen area, mm²	7.1 (1.8)	6.4 (1.4)	0.31
Mean stent area, mm²	7.1 (1.8)	6.4 (1.4)	0.31
Mean vessel area, mm²	16.0 (3.3)	14.9 (3.0)	0.49
Mean peri-stent area, mm²	8.9 (2.2)	8.5 (2.1)	0.68
6-month follow-up			
Mean lumen area, mm²	7.0 (1.8)	6.3 (1.4)	0.35
Mean stent area, mm²	7.1 (1.8)	6.4 (1.4)	0.31
Mean vessel area, mm²	15.8 (2.5)	15.0 (3.3)	0.32
Mean neointimal area, mm²	0.1 (0.1)	0.1 (0.1)	0.16
Mean peri-stent area, mm²	8.7 (1.4)	8.6 (2.4)	0.69
Interval changes			
ΔMean lumen area, mm²	−0.1 (0.1)	−0.1 (0.1)	0.11
ΔMean vessel area, mm²	−0.2 (1.5)	0.1 (1.0)	0.26
ΔMean peri-stent area, mm²	−0.1 (1.5)	0.1 (1.0)	0.31
PES-implanted segments	n = 7	n = 6	
Post-intervention			
Mean lumen area, mm²	5.7 (1.0)	7.0 (1.2)	0.07
Mean stent area, mm²	5.7 (1.0)	7.0 (1.2)	0.07
Mean vessel area, mm²	13.3 (3.2)	14.5 (2.3)	0.45
Mean peri-stent area, mm²	7.6 (2.2)	7.5 (1.3)	1.00
6-month follow-up			
Mean lumen area, mm²	5.2 (1.2)	6.5 (1.6)	0.10
Mean stent area, mm²	5.7 (1.0)	7.0 (1.2)	0.07
Mean vessel area, mm²	13.4 (3.2)	16.6 (2.8)	0.10
Mean neointimal area, mm²	0.5 (0.6)	0.5 (0.8)	0.51
Mean peri-stent area, mm²	7.7 (2.2)	9.6 (1.9)	0.28
Interval changes			
ΔMean lumen area, mm²	−0.5 (0.6)	−0.5 (0.7)	0.51
ΔMean vessel area, mm²	0.1 (0.6)	2.1 (1.2)	0.005
ΔMean peri-stent area, mm²	0.2 (0.6)	2.1 (1.2)	0.005

Results expressed as mean (SD).

disruption of the endothelial layer. We also observed that infused stem cells were preferentially localised in injured segments after balloon injury in rabbit iliac artery.[8] This finding well explained discrepancy in vascular remodelling between stented segments and segments without intervention. In contrast to the segments without intervention, the endothelial layer of stented segments was severely disrupted, leading to infiltration of vascular smooth muscle progenitor cells included in the infused stem cells to participate in tissue growth or vascular remodelling.[11] Furthermore, considering the delayed endothelial recovery with DES, the relative contribution of stem cells to vascular remodelling can be augmented by DES implantation.

The second and third issues are the reason why stem cell therapy induced peri-stent positive remodelling without intraluminal hyperplasia and how to explain the differential outcomes in the PES and SES groups. We can suggest possible mechanisms to explain these two issues. The difference between sirolimus and paclitaxel in pharmacokinetics and antiproliferative action on smooth muscle lineage cells may be a possible explanation. Sirolimus had relatively concentration-independent antiproliferative effects on circulating smooth muscle progenitor cells and vascular smooth muscle cells which were cellular components of medial and neointimal hyperplasia (supplementary fig 1).[10 12] In contrast, antiproliferative effects of paclitaxel showed steep concentration-dependent responses. Thus, in the setting of stem cell therapy, the inhibitory action of paclitaxel would decline in the peri-stent medial area, which is relatively distant from the stent strut, whereas sirolimus would exert concentration-independent antiproliferative effects and exert superior inhibition of cell proliferation at the distant peri-stent medial area. This difference between the transmural distribution of sirolimus and paclitaxel may potentiate the differential inhibitory effects of paclitaxel and sirolimus.[13] However, we cannot distinguish the individual contributions of circulating progenitor cells, resident smooth muscle cells and extracellular matrix or fibrin at the injured site to positive remodelling, so further study is needed to reveal the precise mechanism of positive remodelling observed in our study.

In addition to this experimental evidence, Tanabe *et al* reported that expansive peri-stent positive remodelling occurred after slow and moderate-releasing PES implantation when comparing postprocedural and follow-up IVUS findings in the TAXUS-II study.[14] However, these trends were attenuated at longer-term follow-up.[15] On the basis of this experimental and clinical evidence, there is a possibility that PES may be weaker in preventing positive remodelling in the situation of therapy with G-CSF-mobilised stem cells.

Implication of peri-stent tissue growth or positive remodelling

The most important point is the impact of peri-stent tissue growth or positive remodelling on clinical outcomes. In the previous studies in which peri-stent remodelling was observed, the relation between peri-stent remodelling and neointimal hyperplasia was conflicting. Hoffmann *et al* demonstrated a positive correlation between the extent of tissue growth within the stent and surrounding the stent after bare metal stent (BMS) implantation.[16] In contrast, Nakamura *et al* demonstrated the distinct trade-off between positive remodelling and in-stent hyperplasia after BMS implantation.[17] Nakatogawa *et al* also reported that greater peri-stent positive remodelling after BMS implantation in patients with AMI was associated with less neointimal proliferation and greater luminal gain.[18] However, in the TAXUS-II trial, the IVUS data showed no significant correlation between the extent of peri-stent remodelling and neointimal hyperplasia in either BMS or DES.[14 15] Our data also showed no significant correlation between the extent of peri-stent hyperplasia and neointimal hyperplasia, and there was no association between the presence of peri-stent hyperplasia and clinical outcomes. However, it is still possible that the different biological effects of SES and PES in the setting of stem cell therapy might influence clinical outcome in the longer term, and therefore we believe that long-term follow-up data in large-scale clinical trials are needed to address the issue

of clinical significance of peri-stent tissue growth after DES implantation with stem cell therapy.

Limitations

First, although this IVUS study was planned as a prospective study, it has a small sample size with a considerable rate of drop-out in IVUS evaluation due to the invasive and complex nature of the study. However, characteristics and outcomes of patients enrolled in the IVUS study were very similar to those of patients enrolled in the MAGIC Cell-3-DES study. Second, a higher LDL cholesterol level in the cell infusion group might unfavourably influence vascular remodelling compared with the control group. However, there was no difference in LDL cholesterol between the PES and SES groups, which showed differences in peri-stent positive remodelling. Furthermore, there was no known relationship between LDL cholesterol level and peri-stent remodelling. Third, we evaluated effects of stem cell therapy on vasculature only with relatively short-term follow-up of 6 months. The outcomes should be evaluated with longer-term follow-up.

In conclusion, stem cell therapy with intracoronary infusion of PBSCs mobilised with G-CSF did not aggravate in-stent neointimal hyperplasia after DES implantation or adversely affect de novo lesions of the coronary artery. An interesting finding is that it induced peri-stent tissue growth in the stented segment, especially in patients receiving PES. The clinical implications of this should be further studied.

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