Journal of Cardiology 65 (2015) 298–304

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Two-year vessel healing after everolimus-eluting stent implantation: Serial assessment by optical coherence tomography

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ARTICLE INFO

Article history:
Received 10 March 2014
Received in revised form 26 June 2014
Accepted 3 July 2014
Available online 28 July 2014

Keywords:
Optical coherence tomography
Everolimus-eluting stents
Long-term vessel healing

ABSTRACT

Background: Previous reports have suggested the importance of delayed arterial healing and the development of neoatherosclerosis as major contributors to stent thrombosis and delayed restenosis. The difference of in vivo assessment of long-term vessel healing between first-generation drug-eluting stents and current generation everolimus-eluting stents (EESs) is limited. The aim of this study was to evaluate long-term arterial healing in EES in comparison with the first generation sirolimus-eluting stents (SES).

Methods: We evaluated 31 EES (23 patients) and 8 SES (7 patients) by serial optical coherence tomography at 12 months (mid-phase) and 24 months (late-phase) after stenting and evaluated the change in neointimal thickness (NIT), the percentages of uncovered struts, peri-strut low intensity area (PLIA; region around stent struts homogenously lower-intensity appearance than surrounding tissue), and thrombus.

Results: Although the average NIT showed no significant changes from the mid- to the late-phase follow-up in both EES and SES groups, the change in NIT and minimum lumen area was significantly larger in SES than EES (5.2 ± 29.4 vs. 37.2 ± 48.9; $p = 0.02$, -0.06 ± 0.36 vs. -0.45 ± 0.74; $p = 0.04$, respectively). The incidence of uncovered struts and struts with PLIA of EES was lower than those of SES, at both phases. Stents with in-stent thrombus of EES tended to be lower than that of SES at both phase follow-ups.

Conclusion: Although both SES and EES showed progressive luminal narrowing from the mid- to the late-phase follow-up, the extent of delayed lumen narrowing and delayed neointimal proliferation was significantly less in the second generation EES than the first generation SES. EESs seem to offer sustained stability in efficacy, without sacrificing safety, up to 2 years after implantation.

Introduction

Late stent thrombosis [1] and delayed restenosis [2] have become long-term concerns after drug-eluting stent (DES) treatment. Although these are multifactorial, previous investigators have implicated delayed arterial healing and the development of neoatherosclerosis within neointima as possible underlying mechanisms of these phenomena [3].

Optical coherence tomography (OCT) is a high-resolution intravascular imaging modality and some of these OCT findings (e.g. uncovered struts, malapposed struts, and thrombus formation) have been demonstrated to be associated with stent thrombosis and target lesion revascularization [4,5].

Although several studies have used sequential OCT examination to investigate the time course of arterial healing after first-generation DES implantation [6,7], there is little information about the difference in serial changes in vessel reactions to current generation everolimus-eluting stents (EESs) [8].

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http://dx.doi.org/10.1016/j.jjcc.2014.07.003
0914-5087/

Therefore, the present study focused on comparing the time course of arterial healing after EES and sirolimus-eluting stents (SES) implantation, evaluated by matched serial OCT examinations, in patients with coronary artery disease.

Methods

Study population

We identified 225 consecutive patients treated with SES (Cypher; Cordis Corp., Miami Lakes, FL, USA) between October 2004 (when SES launched in Japan) and May 2010, and 130 patients with EES (XIENCE V, Abbott Vascular, Santa Clara, CA, USA; PROMUS, Boston Scientific, Natick, MA, USA) between January 2010 (when EES launched in Japan) and December 2010.

Of these, 158 patients with SES and 66 patients with EES underwent routine 6–12-month follow-up coronary angiography with OCT examination. Among these, patients who met the inclusion and exclusion criteria were prospectively enrolled in this study for sequential angiographic and OCT examinations. The inclusion criteria for this study were as follows: (a) patients with a de novo coronary lesion (>50% diameter stenosis) treated with SES or EES, who underwent routine 6–12-month follow-up coronary angiography and OCT; (b) native vessel size of 2.5–3.5 mm in diameter, and (c) stable angina or acute coronary syndrome. The exclusion criteria were as follows: (1) patients with ST-elevated acute myocardial infarction, (2) target lesion revascularization during follow-up, and (3) patients unsuitable for coronary angiography due to renal dysfunction or congestive heart failure. Eventually, 8 SES from 7 patients and 31 EES from 23 patients were enrolled in the study. All patients were taking dual antiplatelet therapy with aspirin 100 mg/day and clopidogrel 75 mg/day or ticlopidine 200 mg/day, for at least 6 months after EES implantation.

OCT examination

The OCT examination was performed serially, 6–12 months after stenting as mid-phase follow-up and 24 months after stenting as late-phase follow-up. In the present study, because frequency-domain OCT had not been approved for clinical use in Japan at the time of the mid-term follow-up, time-domain OCT with coronary artery occlusion was used for imaging in the mid- and late-phase follow-up examinations. The OCT examination was performed as previously reported [9]. Briefly, a 0.016-in. OCT catheter (Image Wire, LightLab Imaging, Westford, MA, USA) was advanced to the distal end of the stented lesion. The occlusion balloon (Helios^{TM}, LightLab Imaging, Inc.) was inflated to 0.5 atm at the proximal site of the stented lesion; then lactated Ringer's solution was infused into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5–0.7 mL/s to clear the area of blood. The entire stented length of the lesion was then imaged using an automatic pullback system moving at 1 mm/s.

Quantitative coronary angiography analysis

Coronary angiograms, obtained at baseline, the mid-phase (12 months), and the late-phase (24 months) follow-up, were analyzed using a computer-based system with edge-detection techniques (QCA-CMS5.1, Medis Imaging Systems, Leiden, Netherlands). Late loss was defined as the difference between the minimum lumen diameter (MLD) after the procedure and at the mid-phase follow-up. Delayed late loss was defined as the difference between the MLD at the mid-phase and at the late-phase follow-up.

OCT analysis

Off-line OCT analysis was performed using the dedicated software (LightLab Imaging, Inc.). For quantitative analysis, cross-sectional OCT images were analyzed at 1-mm intervals. We used the distance from the stent edge and landmarks such as side branches to match the location of the cross-sections between the mid-phase and late-phase examinations. The stent and lumen area were measured manually, and the neointimal area was calculated as stent area minus lumen area.

Neointimal thickness was defined as the distance between the stent strut and the lumen surface. An uncovered strut was defined as a strut with a neointimal thickness equal to 0 μm. The frequency of covered and uncovered struts was calculated as the number of those struts divided by the total number of struts for each stent. A malapposed strut was defined as a distance of more than 108 μm in EES and 170 μm in SES between the center reflection of the strut and the vessel wall. EES criterion was determined by adding the actual strut thickness and polymer thickness to the OCT resolution limit (81 μm + 7 μm + 20 μm = 108 μm) [10]. The frequencies of struts with a peri-strut low intensity area (PLIA) and an extra-stent lumen (ESL) were calculated. PLIA was defined as a region around stent struts with a homogeneous lower intensity than the surrounding tissue on OCT images, without significant signal attenuation behind the area [11]. ESL was defined as a lumen external to the stent struts [6].

The frequency of atherogenic neointima (AN) (indicating neoatherosclerosis) and intra-stent thrombus was calculated. AN was defined as neointima containing a diffuse border and a signal-poor region, with the struts underneath invisible because of the marked signal attenuation [12,13]. Intra-stent thrombus was defined as a mass protruding beyond the stent strut into the lumen, with significant attenuation behind the mass [14]. The presence of PLIA, ESL, and intra-stent thrombus required the agreement of two independent experienced observers (T.S. and H.O.). Representative images of cases with AN and thrombus are shown in Fig. 1.

Statistical analysis

The statistical analysis was conducted using the commercially available SPSS software version 16.0 (SPSS Inc, Chicago, IL, USA). Qualitative data are presented as frequencies and quantitative data as mean values ± SD. For continuous variables, comparisons between two groups were performed using a 2-tailed, unpaired *t*-test or the Wilcoxon test. Discrete variables are presented as percentages and comparisons were performed by chi-square analysis or Fisher's exact test. A multivariate logistic regression analysis was done to find out the independent factors for the minimum lumen area (MLA) change and neointimal thickness (NIT) change. A probability value (p) of less than 0.05 was considered significant.

Results

Baseline patient and lesion characteristics

Baseline patient and lesion characteristics were matched between the EES group and SES group (Table 1). There was no statistical difference regarding the percentage of patients under dual antiplatelet therapy at the mid- and late-phase follow-up between the groups.

Angiographic analysis

Although in-stent MLD at the mid-phase follow-up showed no significant difference between EES and SES group, in-stent late loss