Serial Assessment by Optical Coherence Tomography of Early and Late Vascular Responses After Implantation of an Absorbable-Coating Sirolimus-Eluting Stent (from the First-in-Human DESSOLVE I Trial)

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The initial enthusiasm caused by the potent antirestenotic effect of early generation drug-eluting stents was recently plagued by concerns regarding their safety profile. Investigators worldwide were stimulated, therefore, to seek for improvement in drug-eluting stent technology, such as eliminating their permanent polymer blamed for vascular inflammation and delayed healing. Optical coherence tomography (OCT) assessments of stent-vessel interactions are used as a surrogate for vessel healing after DES implantation. Herewith, we report serial OCT assessments of vascular reactions to the implantation of a novel absorbable polymer sirolimus-eluting stent (MiStent). In total, 30 patients were included. At 4-, 6-, and 8-month follow-up, different groups of 10 patients underwent OCT imaging, whereas all the patients had OCT assessments scheduled at 18-month follow-up. A total of 13,569 stent struts were analyzed. Low rates of uncovered (14.34 ± 15.35%, 6.62 ± 10.93%, 3.51 ± 2.87%, and 0.84 ± 1.15%, respectively, p < 0.05 for 8- vs 18-month follow-up) and malapposed (3.74 ± 7.35%, 3.15 ± 6.13%, 0.48 ± 0.56%, and 0.09 ± 0.28%, respectively, p = NS) stent struts coupled with thin and increasingly homogenous neointimal proliferation were demonstrated. Neointimal area increased from 4- to 8-month follow-up (0.46 ± 0.29 and 1.12 ± 0.73 mm², respectively, p < 0.05), whereas no “late catch up” was demonstrated at 18-month follow-up (1.28 ± 0.66 mm², p = NS vs 8-month follow-up). Early tissue maturation and reduction of low signal intensity tissue covering stent struts (8.8%, 3.1%, 0.3%, and 0%, respectively, p < 0.05 for 4- vs 8-month follow-up comparison) were revealed by optical density analysis. In addition, high rates of strut coverage overlaying the ostia of side branches without proliferative pattern were demonstrated. In conclusion, this comprehensive OCT analysis depicted favorable absorbable polymer sirolimus-eluting stent–vessel interactions up to 18-month follow-up. © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;112:1557–1564)

Pathologic investigations suggested that delayed healing, characterized by inflammatory infiltrate and fibrin deposition in vessels treated with drug-eluting stents (DES), is associated with an increased risk of stent thrombosis1,2; therefore, substantial efforts have been devoted to increase DES safety while preserving its anti-proliferative efficacy.3,4 Intravascular optical coherence tomography (OCT) assessments of stent-vessel interactions have been used in vivo as surrogate end points to evaluate the healing process after DES implantation.3–5 The novel absorbable polymer sirolimus-eluting stent (APSES) composed of thin (64 µm) cobalt-chromium struts (MiStent Sirolimus-Eluting Absorbable Polymer Coronary Stent System; Micell Technologies, Durham, North Carolina) was developed with the goal of reconciling antiproliferative efficacy and safety.5 The DESSOLVE I (DES with Sirolimus and a Bioabsorbable Polymer for the Treatment of Patients with De Novo Lesion in the Native Coronary Arteries) trial was the first-in-human study evaluating this APSES platform.6 Herewith, we report the comprehensive analysis of serial OCT images obtained at 4-, 6-, 8-, and 18-month follow-up after the initial experience with APSES implantation in humans.

Methods

The APSES has been previously described.5 The design of the DESSOLVE I trial has been described elsewhere.6 Briefly, it is a first-in-human, prospective, nonrandomized, multicenter study of the new MiStent sirolimus-eluting stent coated with an absorbable polymer. At 4-, 6-, and 8-month follow-up, different subgroups of 10 patients were scheduled to undergo angiography, intravascular ultrasound, and OCT of the target vessel. All patients had OCT assessments scheduled at 18-month follow-up. The study...
The protocol was approved by the institutional review boards of every participating institution, and all patients provided written informed consent.

Images were acquired with a commercially available system (C7-XR OCT Intravascular Imaging System; St. Jude Medical, St. Paul, Minnesota) after intracoronary administration of 200 μg of nitroglycerin through conventional guiding catheters. A 0.014-mm guidewire was positioned distally, and the OCT catheter (C7 Dragonfly, St. Jude Medical, St. Paul, Minnesota) was advanced to the distal end of the stent. The entire length of the region of interest was scanned using the integrated automated pullback device at 20 mm/s. During image acquisition, coronary blood flow was replaced by contrast dye infusion. All images were digitally stored and submitted to core laboratory off-line evaluation (Imaging Core Laboratory, Harrington Heart and Vascular Institute, University Hospitals Case Medical Center, Cleveland, Ohio) and subsequent analysis using proprietary software (St. Jude Medical, St. Paul, Minnesota). All cross-sectional images (frames) were initially screened for quality assessment and excluded from analysis if any portion of the image was out of the screen or the image had poor quality caused by residual blood or sew-up artifact. Side branches occupying >45° of the cross-section were excluded from the formal quantitative analysis, but the stent struts overlying ostia of the side branches underwent binary qualitative evaluation of coverage at every frame (i.e., 0.2-mm interval). The struts overlying side branch ostia underwent qualitative assessment of coverage and were classified as uncovered, covered, or proliferative, as previously described. Strut-level analyses in non-bifurcated segments were performed considering every 3 frames (0.6-mm interval) along the entire target segment. Lumen, stent, and neointimal hyperplasia (NIH) areas and volumes were calculated in a similar fashion at all time points. The center of the luminal surface of the strut blooming was determined for each strut and its distance to the lumen contour was calculated automatically to determine strut-level intimal thickness. Strut malapposition was determined when the negative value of strut-level intimal thickness was higher than the strut thickness, according to the stent manufacturer’s specifications, with the addition of a compensation factor of 20 μm to correct for strut blooming. The blooming compensation factor was determined based on the analysis of 2,250 struts. Highly reproducible measurements for strut apposition and coverage using the described methods have been reported. Qualitative imaging assessment was performed in every frame at all

Figure 1. Normalized optical density (NOD) assessment examples. OCT cross-sectional images (A to C) represent examples of how NOD is calculated. The regions highlighted by the white square are shown in greater detail below each cross section. The values in white correspond to the optical density (mean intensity) of the tissue covering the stent struts, which are automatically calculated after manually drawing a square (i.e., white squares in zoomed images) in the region of interest. The optical density of stent struts (blue values) is obtained in a similar fashion (blue squares). The NOD is finally obtained by dividing tissue by stent strut optical density.
the time points for the presence of abnormal intrastent tissue, which was defined as any mass protruding beyond the stent struts into the lumen, with irregular surface and a sharp intensity gap between mass and neointimal tissue. Calcific neointima was defined as a well-delineated signal-poor region with sharp borders. Lipid-laden neointima was defined as a signal-poor region with diffuse borders. The stented segment was automatically segmented in 2.5-mm intervals (subsegments). A 2.5-mm subsegment with any malapposed strut was regarded as malapposed, whereas if no malapposition was detected in the entire subsegment, then it was counted as fully apposed. To determine longitudinal heterogeneity of uncovered or malapposed struts, as well as of NIH distribution, a coefficient of variation (CV) was assessed for each 2.5-mm subsegment and calculated dividing SD by the mean percentage of uncovered or malapposed struts or NIH thickness. Cross-sectional images were segmented in 360° axial chords between the lumen and the stent contours, and the neointima eccentricity index was calculated as maximum NIH thickness divided by the average value of 360° NIH measurements. An index of 1 represents concentric NIH. The final neointimal eccentricity index was the average of all cross sections within the stented segment. We also evaluated the pixel intensity (optical density) of stent strut covering tissue localized in the inner side of the struts, normalized for the optical density of the stent struts. A good correlation between optical density of stent strut covering tissue/optical density of stent struts (named normalized optical density) and morphologic information provided by both light and electron microscopies has been described previously by our group and others in preclinical models. Randomly chosen stent struts were evaluated at all time points. A region of interest was manually drawn by 2 experienced OCT analysts and the values of optical densities of stent strut covering tissue and stent struts were obtained automatically (Figure 1). The reference value for low signal intensity tissue (LSIT) was obtained from preclinical data. A threshold of 0.610 was used to maximize specificity (95%).

The principle analysis was conducted using SAS 9.2 (SAS Institute Inc, Cary, North Carolina). Continuous variables are presented as mean ± SD and categorical variables are presented as number (percentage). For continuous variables, comparisons between 4-, 6-, and 8-month follow-up were made with 1-way analysis of variance, using Tukey post hoc test for the 3 individual-group differences. Comparison results were further confirmed by nonparametric Kruskal-Wallis test using post hoc Mann-Whitney U tests with Bonferroni correction. Categorical variables were compared using Fisher’s exact test with Bonferroni correction. The generalized estimating equations model with exchangeable correlation structure to account for the repeated measure within each subject was used for the comparison between 8- and 18-month follow-up. To estimate differences between different time points at strut level, specifically for LSIT-covered strut rate comparison, a multilevel mixed model, which can address random effects at frame and subject levels, was used.

Results

Thirty patients were included in the study. Clinical and baseline angiographic characteristics are listed, respectively, in Tables 1 and 2. OCT imaging was conducted
Planar and volumetric analysis

Strut-level analysis

- Total stent length (mm): 17.48 ± 5.99
- Total frames: 27.50
- Not analyzable frames (%): 8.55

Patients, n

- 4 Months: 10
- 6 Months: 9
- 8 Months: 9
- 18 Months: 27

Lesions, n

- 4 Months: 10
- 6 Months: 9
- 8 Months: 9
- 18 Months: 27

Stents, n

- 4 Months: 10
- 6 Months: 10
- 8 Months: 9
- 18 Months: 28

Lesions, n

- 4 Months: 10
- 6 Months: 9
- 8 Months: 9
- 18 Months: 27

- Comparison between 4- and 8-month follow-up, p < 0.05.
- Comparison between 4- and 6-month follow-up, p < 0.05.
- Comparison between 4- and 18-month follow-up, p < 0.05.
- Threshold used to characterize LSIT was 0.610 based on preclinical data (specificity 95%).

Table 3
Optical coherence tomographic assessments at 4-, 6-, 8-, and 18-month follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>4 Months</th>
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<td>9</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>Stents, n</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>Total stent length (mm)</td>
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<td>18.51 ± 5.66</td>
<td>20.84 ± 4.12</td>
<td>18.56 ± 5.61</td>
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<tr>
<td>Total frames</td>
<td>27.50</td>
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<td>32.22 ± 7.36</td>
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<tr>
<td>Not analyzable frames (%)</td>
<td>8.55</td>
<td>11.00 ± 7.65</td>
<td>9.49 ± 5.66</td>
<td>10.56 ± 8.61</td>
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</table>

Strut-level analysis

Uncovered struts (%) 14.34 ± 15.35
Uncovered, malapposed struts (%) 3.74 ± 7.35
NIH (μm) 71.73 ± 39.78

Patients with >10% uncovered struts, n (%) 9/286 (3.1) 1/353 (0.3) 9/570 (1.6)

Subsegments with any malapposed struts (%) 36.45 26.77 ± 35.59 10.00 ± 11.15 2.12 ± 5.72

Maximum length of malapposed segment (mm) 5.14 ± 10.64 7.27 ± 3.74 14.99 ± 6.31 17.93 ± 9.18

CV of NIH area in 2.5-mm subsegment (%) 52.53 131.40 119.04 113.75 45.62
CV of malapposed struts in 2.5-mm subsegment (%) 131.40 79.49 55.71 74.9 ± 2.87
CV of uncovered struts in 2.5-mm subsegment (%) 114.30 74.9 ± 2.87 148.29 ± 63.51 137.98 ± 56.69

Planar and volumetric analysis

Stent area (mm²) 6.27 ± 1.58 6.24 ± 3.39 7.44 ± 2.08 7.49 ± 2.42
Lumen area (mm²) 5.97 ± 1.72 7.62 ± 3.41 6.42 ± 1.55 6.23 ± 2.34
Minimal lumen area (mm²) 5.07 ± 1.55 5.75 ± 3.21 5.05 ± 1.36 5.03 ± 2.14
Neointimal area (mm²) 0.46 ± 0.29† 0.81 ± 0.29 1.12 ± 0.73† 1.28 ± 0.66

CV of NIH area in 2.5-mm subsegment (%) 52.53 79.49 55.71 74.9 ± 2.87
CV of malapposed struts in 2.5-mm subsegment (%) 131.40 79.49 55.71 74.9 ± 2.87
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Optimal coherence tomographic assessments at 4-, 6-, 8-, and 18-month follow-up. In (A) and (B), graphical representations of uncovered and malapposed struts distribution (patient-level), respectively, at different FU time points are demonstrated.

Figure 2. Distribution of uncovered and malapposed stent struts at 4-, 6-, 8-, and 18-month follow-up (FU). In (A) and (B), graphical representations of uncovered and malapposed struts distribution (patient-level), respectively, at different FU time points are demonstrated.

No patients developed serious noncardiac diseases. A total of 13,569 stent struts equally distributed in different time
points were analyzed (Table 3). In addition, 233 struts overlying side branch ostia in bifurcation segments were evaluated qualitatively for coverage status.

Low rates of uncovered stent struts were demonstrated early, with further reduction at 18-month follow-up. Likewise, stent strut malapposition was low at early time points, and a trend toward additional reduction was demonstrated at 18-month follow-up (Figure 2 and Table 3). Maximum length of uncovered and malapposed struts followed the same pattern of vascular reaction (Table 3). Abnormal intrastent tissue was identified at 6 months in 1 asymptomatic patient who was compliant with dual antiplatelet therapy and disappeared at 18-month follow-up. Among struts overlying side branch ostia, the percentage of uncovered and malapposed struts followed the same pattern of vascular reaction (Table 3). Abnormal intrastent tissue was identified at 6 months in 1 asymptomatic patient who was compliant with dual antiplatelet therapy and disappeared at 18-month follow-up. Among struts overlying side branch ostia, the percentage of uncov-

The CV for uncovered struts and NIH area was significantly reduced from 8- to 18-month follow-up, whereas the CV for malapposed struts exhibited a similar, although nonsignificant, reduction for the same interval (Table 3).

Significant increase in normalized optical density was observed between 4- and 6-month follow-up, and reduction in the presence of LSIT-covering stent struts was observed between 4- and 8-month follow-up (Table 3).

Discussion

The main findings of this comprehensive OCT assessment of the initial experience with APSES implantation in humans were (1) high rates (>90%) of stent coverage early after deployment of APSES with further improvement at 18-month follow-up, (2) low rates of malapposed stent struts at all time points, (3) sustained and homogenous inhibition of NIH up to 18 months, and (4) early tissue maturation with virtual absence of LSIT at 8 months after procedure based on tissue optical density analysis.

Most OCT studies focused on stent evaluation at single time points. The present study design, however, provides an opportunity to assess early and late vascular responses and understand the process of vascular healing overtime. Furthermore, this study evaluated the entire spectrum of the healing process after DES implantation, which included serial assessments of NIH, coverage,
apposition, and tissue characteristics in a longitudinal fashion. Our findings suggested excellent vascular response to APSES implantation as early as 4 months after procedure. In addition, the long-term OCT data (i.e., 18-month follow-up) provided unique insights into late vascular response and neointimal proliferation, which has been a concern for earlier generation DES with the observation of neatherosclerosis development. In our series, we were able to identify 2 cases (7.4%) of newly developed lipid-laden neointima (i.e., neatherosclerosis) in the distal edge (4 frames of lipid-laden neointima per patient) of 2 stents that were not observed in early time points but were present at 18-month follow-up. Although these data illustrate the importance of serial imaging to properly diagnose neatherosclerosis, they confirm favorable APSES-vessel interactions by revealing remarkably lower rates of neatherosclerosis after its implantation compared with what has been previously described for other DES. Longer term follow-up and larger sample sizes are warranted to confirm our findings.

The rationale for the assessment of vascular response to DES as a surrogate for safety is based on postmortem data suggesting that delayed healing with the presence of uncovered struts is associated with stent thrombosis. In addition, in vivo studies using intravascular ultrasound imaging linked stent strut malapposition with stent thrombosis. Guagliumi et al reported higher rates of uncovered and malapposed stent struts in patients with stent thrombosis compared with controls without stent thrombosis. The present study provides the first detailed evaluation of vascular response to APSES implantation in humans. Using OCT imaging, we were able to demonstrate very low rates of uncovered and malapposed stent struts early after therapy (i.e., 4 months). The reduced malapposition volumes further suggest a favorable vascular response to APSES implantation (Table 3). Recently described as an independent predictor of DES thrombosis, the maximum length of uncovered struts was considerably short at 6 months and demonstrated incremental improvement at 18 months after APSES implantation (Table 3). Taken together, the data suggest that although the healing process seems to be advanced at 4 months, it continues to improve over time. Vascular reaction heterogeneity has been recently associated with stent thrombosis, but no thresholds have been established to prospectively determine risk profiles. In the present study, we evaluated vascular response heterogeneity using CV of uncovered and malapposed struts and demonstrated incremental homogeneity of vascular reaction to APSES over time (Table 3). Whether these findings might improve clinical safety of APSES remains to be determined.

Figure 5. Demonstration of neatherosclerosis (lipid-laden neointima). In (A), a normal vessel is depicted in the distal reference and the stented segment demonstrates thin NIH at 8-month follow-up (B). The same region at 18-month follow-up demonstrates the formation of a lipid plaque (white asterisks, Al and BI), whereas stent strut visualization is impaired by the lipid-laden tissue (white arrow).
We had previously demonstrated the absence of late neointimal proliferation with APSES using longitudinal OCT assessments in a preclinical model. Nevertheless, more predictable vascular response in nondiseased swine precluded definitive conclusions. In the present study, thin and reduced NIH areas and volumes were demonstrated after APSES implantation; in addition, neutralization of NIH growth was shown from 8- to 18-month follow-up. At the cross-sectional level, homogeneity of tissue proliferation in growth was shown from 8- to 18-month follow-up. After APSES implantation; in addition, neutralization of NIH and reduced NIH areas and volumes were demonstrated available in the present study, we decided to use the broader cross-sectional level, homogeneity of tissue proliferation in growth was shown from 8- to 18-month follow-up. Nevertheless, longer term OCT assessments are warranted to rule out the possibility of additional NIH growth after 18-month follow-up.19 Delayed healing and the presence of peristrut fibrin were previously correlated with stent thrombosis by histopathology.2 We had previously demonstrated tissue maturation and reduction of LSIT content covering APSES struts over time in animal models.5 It is important to emphasize, however, that LSIT identified by OCT can correspond to several different types of abnormal vascular response.27,28 Therefore, because no histopathologic confirmation was available in the present study, we decided to use the broader term “low signal intensity” instead of “fibrin”. Very early tissue maturation, with significant increase in normalized optical density from 4- to 6-month follow-up coupled with a progressive reduction of LSIT, suggests a satisfactory healing profile of APSES (Table 3). Although OCT surrogates for vascular healing suggest a good safety profile of APSES up to 18-month follow-up, in this pilot trial, long-term clinical follow-up in a large population is warranted to validate these findings. The lack of imaging in every time point for all patients represents a limitation. However, our study design of OCT early assessments in different subgroups with all patients having late OCT assessments allows characterization of vascular response over time in different periods while minimizing the inherent risks of repeated invasive interventions, exposure to x-ray, and injection of iodinated contrast. Finally, a direct comparison between APSES and a conventional stent is lacking and would be an important reference for the present results; nevertheless, the primary objective of DESSOLVE I study was to provide preliminary evaluation of the safety and efficacy of APSES and to provide guidance for future randomized trial designs.

Disclosures

G.F.A., has received consulting fees from St. Jude Medical. H.G.B. has received honoraria grants from St. Jude Medical, Inc. J.O. has received research/grant support and consulting/educational honoraria from Abbott Vascular and Boston Scientific Corporation. D.D. is a consultant for Micell Technologies. M.A.C. is on the Speakers’ Bureau of and is a consultant for Daiichi-Sankyo, St. Jude, Boston Scientific Corporation, Sanofi-Aventis, Eli Lilly, and Medtronic; he is also on the Speakers’ Bureau of and is a member of the Scientific Advisory Boards for Abbott, Cordis, LightLab Imaging, and Scitech. All other authors have reported no conflicts of interest.


