Vascular response towards biodegradable sirolimus-eluting polymeric scaffolds in the porcine model

Abstract: In this study, PLLA-based sirolimus-eluting polymer scaffolds and permanent bare-metal stents (316L) were implanted interventionally into both common carotid arteries (CCA) of 6 female pigs via the left common iliac artery (8F-sheath). The pigs were administered dual antiplatelet drugs peroral starting 3 days before the procedure until the end of the study. Stented CCA segments were explanted after 12 weeks, and processed for quantitative histomorphometry, and estimation of vascular inflammation and injury scores. SIR/polymer scaffolds showed a decreased residual lumen area and higher restenosis after 12 weeks (4.45 ± 2.23 mm² and 61.68 ± 22.39%) as compared to the 316L reference stent (16.53 ± 1.23 mm² and 6.65 ± 1.30%). After 12 weeks, inflammation score and vascular injury score were higher in the SIR/polymer group (1.90 ± 1.15 and 1.26 ± 0.87) compared to the 316L group (0.57 ± 0.37 and 0.83 ± 0.34).

Keywords: biodegradable polymeric scaffold, drug, experimental pig study, carotid artery stenting

Introduction

Fully biodegradable polymeric scaffolds represent a potential alternative to permanent metal stents, but to date, human experience with such devices is limited. The first human coronary application of an absorbable drug-eluting-stent (DES), the BVS, was reported in 2007 [1]. A larger size of the Igaki-Tamai stent without drug elution, suitable for peripheral vessels was successfully investigated in the PERSEUS clinical trail [2]. In addition to biodegradable polymeric scaffolds, application of absorbable magnesium stents was shown in human coronary and peripheral vessels [3,4]. However, after a long-term follow-up, data of the Adsorb-BVS showed higher incidence of scaffold thrombosis and target lesion failure and finally had to be withdrawn from the market in the meantime.

The aim of this study was to evaluate feasibility and biocompatibility of a novel SIR-loaded PLLA-based polymer scaffold for peripheral vascular application in the non-diseased porcine carotid artery model after 12 weeks.

Materials and methods

2.1 Scaffolds

The biodegradable PLLA-based sirolimus-eluting polymer scaffolds used in this study were developed, produced and tested in vitro at the Institute for Biomedical Engineering at Rostock University Medical Center [5,6]. SIR-loaded biodegradable scaffolds (5.0 x 20 mm with an I.D. of 2.2 mm, wall thickness of 250 µm) were implanted using a 5.0 x 40 mm PTA balloon catheter (Passeo-35:5/40/130, Biotronik
SE & CO. KG, Berlin, Germany). Therefore, the SIR-PLLA-based polymer scaffolds were mounted manually on the balloon catheter, predilated extracorporeally with 1 bar and dilated in situ with a pressure of 8 bar for 1 min.

Commercial permanent bare-metal stent systems made from medical-grade stainless steel (316L) and coated with amorphous silicon carbide (Dynamik, Biotronik SE & Co. KG) with a nominal dimension of 5.0 x 25 mm (wall thickness: 160 µm) were used as controls. Metal stents were deployed instantaneously, using inflation pressure of 9 bar.

2.2 Animals and experimental procedure

Animal experiments were approved by the governmental ethical board for animal research (Landesamt für Landwirtschaft, Lebensmittelsicherheit und Fischerei, Mecklenburg-Vorpommern, Germany; No: 7221.3-1.1-027/12) and were carried out in accordance with the EU-directive 2010/63/EU. Six young adult German Landrace pigs with a mean body weight (BW) of 27.2 ± 1.9 kg were the subjects of this study.

Animal preparation and stent implantation was performed as described previously [7]. A total of 12 stents were implanted interventionally into both CCA. After 12 weeks, the pigs were euthanized in deep sedation, and the stented CCA were surgically explanted, and processed for quantitative histological and histomorphometric analysis using hematoxylin & eosin (H&E), as described in [8].

Vascular injury was semi-quantitatively evaluated as described by Schwartz et al. [9]. Inflammatory response was categorized as described by Kornowski et al. [10].

2.3 Statistical analysis

Calculations were performed using SigmaPlot 12.0 (Systat Software Inc., Richmond, CA, USA). Differences between two groups were compared using t-test for normal distributed values or the Mann-Whitney Rank Sum test for nonparametric data. Results are presented as mean ± standard deviation (SD). A p-value <0.05 was considered statistically significant.

3 Results

All animals survived until the end of the study without developing neurological complications. In general, no wound complications were observed. The animals exhibited a weight gain of 45.5 ± 7.5 kg within the 12-week period. During preparation, stent implantation and stent explantation all pigs were hemodynamic stable with a heart rate of 88 ± 12 bpm and a mean arterial pressure of 54 ± 12 mmHg. No aberration was observed in blood parameters between stent implantation and stent explantation.

All stents were successfully implanted. After 12 weeks four out of six SIR/polymer scaffolds were dislocated distally. In both study groups all scaffolds were patent on histological analysis without any signs of excessive recoiling or collapse. In all H&E slices the deployed stent cross section was intact, showing a circular shape (Figure 1).

Vascular injury scores demonstrated only mild vascular trauma for all stents (SIR/polymer: 1.26 ± 0.87; 316L: 0.83 ± 0.34; p=0.54). Inflammation reaction was significantly higher in the SIR/polymer scaffolds compared to 316L (1.89 ± 1.15)

Table 1 presents geometric areas of scaffolds (mean ± SD) in stented porcine carotid arteries after 12 weeks of stent implantation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>316L</th>
<th>SIR/polymer</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>external elastic lamina area (mm²)</td>
<td>21.13 ± 1.4</td>
<td>16.75 ± 2.76</td>
<td>.017</td>
</tr>
<tr>
<td>internal elastic lamina area (mm²)</td>
<td>17.71 ± 1.34</td>
<td>12.04 ± 1.56</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lumen area (mm²)</td>
<td>16.53 ± 1.23</td>
<td>4.45 ± 2.23</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stent area (mm²)</td>
<td>3.64 ± 0.16</td>
<td>1.68 ± 0.16</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neointimal area (mm²)</td>
<td>1.18 ± 0.27</td>
<td>7.59 ± 3.23</td>
<td>.004</td>
</tr>
<tr>
<td>Area stenosis (%)</td>
<td>6.65 ± 1.30</td>
<td>61.68 ± 22.39</td>
<td>.004</td>
</tr>
</tbody>
</table>

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versus $0.57 \pm 0.37$; $p=0.03$). No differences between proximal and distal sections were detected in all H&E slices.

4 Discussion

Due to a higher wall thickness, appeared the SIR/polymer scaffolds showed a decreased residual lumen area and higher restenosis after 12 weeks as compared to the 316L reference stent. Inflammation score and vascular injury score were higher in SIR/polymer compared to the 316L.

Smaller residual luminal areas in the SIR/polymer scaffolds might have been caused by tissue ingrowth into the larger strut interspaces due to higher strut thickness (stent area) in this group. This limitation needs to be addressed in future work on the stent design.

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Author Statement

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