MAHOROBA, first-in-man study: 6-month results of a biodegradable polymer sustained release tacrolimus-eluting stent in de novo coronary stenoses

Yoshinobu Onuma1, Patrick Serruys1*, Peter den Heijer2, Kaiyum Sheik Joesoef3, Henricus Duckers1, Evelyn Regar1, Neville Kukreja1, Shuzou Tanimoto1, Hector M. Garcia-Garcia4, Heleen van Beusekom1, Willem van der Giessen1, and Takuji Nishide5

1Thoraxcenter, Erasmus Medical Center, Ba-583, s-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands; 2AMPHIA Hospital, Breda, The Netherlands; 3Medisch Centrum Rijnmond Zuid, Rotterdam, The Netherlands; 4Cardialysis B.V., Rotterdam, The Netherlands; and 5Kaneka Corporation, Osaka, Japan

Received 8 September 2008; revised 5 February 2009; accepted 11 March 2009; online publish-ahead-of-print 30 April 2009

Aims
To report the 4-month angiographic and 6-month clinical follow-up in first-in-man study using the tacrolimus-eluting bioabsorbable polymer-coated cobalt–chromium MAHOROBA\textsuperscript{TM} stent.

Methods and results
A total of 47 patients with either stable angina or unstable angina, or silent myocardial ischaemia, based on a de novo coronary stenosis that could be covered by a single 18 mm stent in a native coronary artery with a diameter between 3.0 and 3.5 mm were enrolled at three sites. The primary endpoint was in-stent late loss at 4 months. The secondary endpoints include %volume obstruction of the stents assessed by intravascular ultrasound (IVUS) at 4 months and major adverse cardiac events (MACE) at 6 months. Forty-seven patients were enrolled. Procedural success was achieved in 97.9%. At 4-month follow-up, in-stent late loss was 0.99 \(\pm\) 0.46 mm, whereas in-stent %volume obstruction in IVUS was 34.8 \(\pm\) 15.8%. At 6 months, there were no deaths, but 2 patients suffered from a myocardial infarction and 11 patients required ischaemia-driven repeat revascularization. The composite MACE rate was 23.4%.

Conclusion
This tacrolimus-eluting stent failed to prevent neointimal hyperplasia, despite the theoretical advantages of the tacrolimus, which has less inhibitory effects on endothelial cells than smooth muscle cells.

Keywords
Tacrolimus-eluting stent • First-in-man study • Drug-eluting stent • Coronary artery disease

Introduction
Sirolimus-eluting stents (SEs) and paclitaxel-eluting stents (PESs) have markedly reduced the rate of in-stent restenosis and late lumen loss compared with bare-metal stents (BMSs), resulting in a significant reduction in repeat revascularizations. Accordingly, percutaneous coronary intervention (PCI) using drug-eluting stents (DESs) has been accepted as the most effective treatment option for de novo coronary artery disease.

However, enthusiasm for this technology has recently been dampened by concerns about late stent thrombosis, an event often associated with lethal consequences. Delayed re-endothelialization after DES has been suggested as one of the plausible causes of late stent thrombosis.\textsuperscript{2–4} Pathological autopsy studies also support the hypothesis of delayed endothelialization, showing an association between lack of neointimal strut coverage after DES implantation and stent thrombosis. Localized hypersensitivity reactions to the durable polymer coating and/or to the drug
itself may also theoretically add to stent thrombosis. Furthermore, endothelial dysfunction after DES has lately attracted considerable attention. Recent reports suggest that DES may impair endothelial responses to acetylcholine or exercise-mediated vasodilation in humans.

Tacrolimus is a macrolide immunosuppressant drug licensed for prophylaxis of rejection in recipients of organ transplantation. The intracellular receptors are the FK binding proteins (FKBP, including FKBP12): the tacrolimus–FKBP complex binds to inhibit the calci-neurin–calmodulin complex, which suppresses proliferation of T-cells, smooth muscle cells (SMCs), and endothelial cells (ECs). Tacrolimus has a much less inhibitory effect on SMC and EC than sirolimus, but tacrolimus depresses EC less than SMC. These results suggest that tacrolimus may allow better re-endothelialization than sirolimus if proper concentrations for suppressing SMC proliferation are used. Furthermore, unlike sirolimus or paclitaxel, tacrolimus does not affect the tissue factor and e-NOS expression, which might attenuate the risk of stent thrombosis.

A poly D, L-lactide-co-glycolide (PLGA) polymer with sustained drug release for several months was employed to maintain high tissue concentration of tacrolimus. This polymer coating is fully absorbable and theoretically minimizes adverse effect, such as possible hypersensitivity reactions, caused by the permanent presence of a durable polymer. In a porcine model, the MAHOROBA stent (Kaneka, Osaka, Japan) demonstrated early re-endothelialization and reduction of neointimal thickening up to 90 days after the implantation. Conversely, it has yet to be demonstrated that the biodegradation of the polymer in human atherosclerotic vessels does not in itself induce an inflammatory and proliferative response.

The objective of the MAHOROBA I, first-in-man (FIM) study was to test the safety and feasibility of the MAHOROBA™ stent to treat de novo coronary lesions.

Methods

Study design and patient selection

The study enrolled 47 patients at three participating sites in The Netherlands. The local Ethics Committee approved the protocol for each study site, and all patients gave written informed consent before the procedure. Patients over 18 years of age were eligible, provided they had stable angina, unstable angina, or silent myocardial ischaemia with a de novo coronary artery lesion with >50 and 100% stenosis of a length that could be covered by a single 18 mm stent with a diameter between 3.0 and 3.5 mm in one or two major epicardial arteries. The second lesion should fit with inclusion/exclusion criteria and be treated with the same study stent. Patients were not eligible for enrolments if they had an evolving acute myocardial infarction (MI) within 72 h, renal dysfunction (serum creatinine >2.0 mg/dL), a total occlusion with a TIMI flow of 0 or 1, low left ventricular ejection fraction (<30%), a platelet count of <100 000 cells/mm³ or >700 000 cells/mm³, a white blood cell count of <3000 cells/mm³, previous drug-eluting or BMS implantation in the target vessel, a target lesion supplied by an arterial or venous bypass graft, a heavily calcified lesion, a bifurcation lesion involving a side branch >2.0 mm in diameter with an ostial disease, unprotected left-main disease, planned PCI within 60 days after trial stent implantation, planned surgery within 6 months after stent implantation, stroke or transient ischaemic attack within the prior 6 months, a known allergy to aspirin, clopidogrel, cobalt–chromium alloy, heparin, tacrolimus (or similar drugs), or contrast agents that cannot be adequately premedicated.

The MAHOROBA stent

The MAHOROBA tacrolimus-eluting stent (TES) comprises a drug-eluting PLGA coating and a cobalt–chromium (CoCr) stent with a strut thickness of 75 μm, as previously described. The stent has an open-cellular balloon-expandable design and consists of two helical coils inter-crossed with two phase-different links on each turn, in which each link deviates diagonally along the longitudinal axis (Figure 1). The entire abluminal surface of the stent is coated with a fully biodegradable PLGA polymer matrix. The molecular weight of the PLGA polymer was 84 000 Da. The mass ratio of the drug and polymer was 20.6 and 79.4 wt%, respectively. The dose density of tacrolimus and the polymer was 0.94 and 3.58 μg/mm², respectively. The purity of the polymer was over 99.9%. The PLGA polymer was proven by compliance with the ISO 10093s. In the porcine artery model, the PLGA degrades and disappears completely in 6 months. Tacrolimus is released continually for several months and completely resolves with PLGA degradation.

Study procedure

Lesions were treated using standard interventional techniques with mandatory pre-dilatation prior to stent implantation. The following sizes of MAHOROBA stent were used in the study: 18 mm length and either 3.0 or 3.5 mm diameter. Intravascular ultrasound (IVUS) was performed after angiographically optimal stent placement and was repeated if additional post-dilatation was required. Treatment

Figure 1  (A) A photograph of MAHOROBA tacrolimus-eluting stent. (B) A schematic view of the stent structure. Two helical coils inter-cross with two phase-different links. Blue circles and arrows indicate that each link deviates diagonally along the longitudinal axis.
with aspirin, at a minimal dose of 100 mg per day, was started prior to procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered at least 6 h before the procedure, followed by 75 mg daily for at least 13 months.

**Follow-up**

Patients were evaluated clinically at 30 days and 4 months with further evaluation scheduled at 9 and 12 months followed by annual evaluation out to 5 years: patients were asked specific questions about major cardiac adverse events and the interim development of angina according to the Canadian Cardiovascular Society classification of stable angina. Angiographic and IVUS evaluations were performed at 4 months.

**Quantitative coronary angiography**

Quantitative coronary angiography (QCA) analyses were performed by a corelab (Cardialysis B.V., Rotterdam, The Netherlands) with the CAAS II analysis software (Pie Medical B.V., Maastricht, The Netherlands). In each patient, the stented segment and the peri-stent segments defined by a length of 5 mm proximal and distal to the stent edge were analysed. The following QCA parameters were computed: minimal luminal diameter (MLD), reference diameter obtained by an interpolated method, and percentage diameter stenosis. Binary restenosis was defined in every segment (proximal, distal, and stent) as diameter stenosis ≥50% at follow-up. Stent-to-artery ratio was calculated as a mean diameter of the last balloon at the highest pressure divided by the baseline reference vessel diameter. Late loss was defined as the difference between MLD post-procedure and MLD at follow-up. Results are presented as means using matched pair of angiographic views using multiple X-ray views.

For the assessment of acute stent recoil, two sequential angiographic images were analysed: first an image of the complete expansion of the largest balloon at the highest pressure, whereas the second was an image immediately after the final balloon deflation. These two images were analysed in the same angiographic projection. When the stent delivery balloon was used for stent expansion, QCA measurements were performed between the markers of the stent delivery balloon and within the deployed stent markers. Acute stent recoil was calculated as previously described.\(^{17–19}\)

**Intravascular ultrasound**

All cases were imaged with a 2.5 F Atlantis SR pro imaging 40 MHz catheter (Boston Scientific, Santa Clara, CA, USA). Post-procedure and at follow-up, stented culprit vessel segments were examined with mechanical IVUS using automated pullback at 0.5 mm per second. The coronary segment was examined by IVUS beginning 5 mm distal to and extending 5 mm proximal to the stented segment. A validated offline quantitative computer-based IVUS software was used for semi-automated three-dimensional reconstruction and analysis (CURAD Vessel analysis, Wijk bij Duurstede, The Netherlands).\(^{20}\) The lumen, stent boundaries, and the external elastic membrane were detected in longitudinal reconstructed views. In order to obtain a smooth appearance of the vessel wall structures in the longitudinal views, a retrospective image-based gating method was applied (e.g. Intelligate\(^{21}\)).

The volumetric parameters of the stent, lumen, and obstruction [e.g. neointima hyperplasia (NIH)] volume and percentages were calculated as:

\[
\text{Stent Volume} = \sum_{i=1}^{n} (\text{Stent Area}(i)) \times H,
\]

where Stent Area\((i)\) is the stent area in one of the cross-sections of the stent, \(n\) the number of cross-sections, and \(H\) the distance between two consecutive cross-sections.

\[
\text{Lumen Volume} = \sum_{i=1}^{n} (\text{Lumen Area}(i)) \times H,
\]

where Lumen Area\((i)\) is the lumen area in one of the cross-sections of the stent. The other parameters are similar as described in the above formula.

\[
\% \text{NIH Obstruction} = \frac{\text{NIH Volume}}{\text{Stent Volume}} \times 100\%.
\]

Incomplete apposition was defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut by ultrasound, whereas late acquired incomplete apposition was defined as incomplete apposition of the stent at 4-month follow-up which was not present at post-procedure.

**Clinical endpoint definitions**

Target vessel (or lesion) revascularization was considered to be ischaemia-driven if the target vessel (or lesion) diameter stenosis ≥50% by core laboratory quantitative analysis with ischaemic symptoms or with objective signs of ischaemia at rest or during exercise test, or a target vessel (or lesion) diameter stenosis ≥70% with or without documented ischaemia. Major adverse cardiac events (MACE) was defined as the composite of cardiac death, any MI, or ischaemia-driven target lesion revascularization (TLR). Spontaneous MI was defined as either a typical rise and gradual fall (Troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with ischaemic symptoms, development of new pathological Q-waves on the ECG or ECG changes indicative of ischaemia, or pathological findings of an acute MI, or development of new pathological Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event.\(^{22}\) Stent thrombosis was prospectively adjudicated using the Academic Research Consortium definitions.\(^{23}\) Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation of thrombosis.

**Study endpoints**

The primary study endpoint was in-stent late loss at 4 months as measured by QCA. Angiographic secondary endpoints include in-segment late loss, binary restenosis rate, percentage diameter stenosis, and proximal and distal late loss at 4 months. Secondary IVUS endpoints at 4 months include minimal lumen area, stent volume, luminal volume, intrastent neointimal volume, %volume obstruction, incomplete stent apposition, and plaque volume behind the stent struts. Secondary clinical endpoints at 6 months included all-cause death, MI, coronary artery bypass surgery, TLR, definite stent thrombosis, and MACE.\(^{23}\)

**Statistical analysis**

Continuous variables are presented as means ± standard deviation, and categorical variables are presented as counts and percentages. Paired comparisons between post-procedure and 4-month follow-up...
were done by a Wilcoxon’s signed rank test. All statistical tests were two-tailed and a P-value of <0.05 was considered as statistically significant. The current study is a FIM and single-arm study, and was designed to provide preliminary hypothesis-generating observations for further studies. The sample size was not defined on the basis of an endpoint hypothesis but rather to provide some information about the device efficacy and safety. The sample size requirement was established by the assessment of the minimum number of patients needed to provide reliable and non-trivial results, but is in range of the test group of the FIM trials of the SES (n = 45). Statistical analysis was performed with SAS 8.2 (SAS Institute Inc., NC, USA).

The role of funding source
The study was sponsored by Kaneka (Osaka, Japan). In collaboration with the investigators, the sponsor designed the study. Data collection and data analysis were done by an independent clinical research organization (Cardialysis B.V.). The sponsor had no role in data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patient characteristics
Forty-seven patients were included between May 2007 and November 2007. The baseline clinical characteristics are presented in Table 1. The average age of the patients was 61.1 ± 9.4 years, whereas 19.1% were diabetic and 66.0% were male. Procedure success was 97.9% since, in one patient, the MAHOROBA stent did not cross the lesion due to severe calcification. Since the follow-up is planned up to 5 years, the follow-up will be accomplished in November 2012.

Quantitative coronary angiography analysis
Angiographic follow-up at 4 months was achieved in 41 patients (Figure 2). The angiographic parameters with matched pair analysis for phase and projection at baseline, post-procedural, and follow-up angiography (n = 37) are presented in Table 2. Table 3 presents the results of QCA parameters related to acute stent recoil assessment. Acute absolute recoil was 0.22 ± 0.20 mm. At 4 months, the mean in-stent late loss, in-stent percentage diameter stenosis, and the rate of binary angiographic restenosis were 0.99 ± 0.46 mm, 38.66 ± 20.79%, and 26.7%, respectively. Figure 3 demonstrates the cumulative frequency of in-stent MLD immediately after the index procedure and after 4 months.

Intravascular ultrasound evaluation
At 4 months, IVUS evaluation was performed in 40 patients. The results are tabulated in Table 4. A significant reduction of luminal volume was observed (187.4 ± 93.4 mm³ at post-procedure vs. 123.5 ± 67.2 mm³ at follow-up, P < 0.0001) with %volumetric obstruction of 34.78 ± 15.76%.

Incomplete stent strut apposition at baseline was reported in 16 of 46 (34.8%) patients, and this was resolved in 10 and persisted in 7 patients at 4-month. There were three cases of late acquired incomplete apposition based on the IVUS definition of malapposition of at least one stent strut separated from the vessel wall. According to a methodology, previously reported by our group, the malapposed volume at follow-up was 3.99 mm³ in median (inter-quartile range 1.88–7.39).26

Major adverse cardiac events
Major adverse cardiac events are listed in Table 5. There were two cases of MI: one patient suffered a non-Q-wave MI at 64 days after the implantation of one MAHOROBA stent in the proximal left anterior descending artery, whereas the other experienced a non-Q-wave MI at 4 days after the procedure with angiographically proven definite stent thrombosis in the proximal left circumflex. Both patients were taking dual antiplatelet therapy at the time of MI. The latter patient experienced second TLR at 124 days due to restenosis of the MAHOROBA stent. There were other nine
cases of ischaemia-driven TLR (ID-TLR). In total, MACE rate (cardiac death, target-vessel MI, or ID-TLR) at 6 months is 23.4% (11/47).

Discussion

The efficacy of tacrolimus in inhibiting neointimal proliferation has been demonstrated in preclinical studies. Wieneke et al.27 in an in vivo study using rabbit iliac artery model demonstrated that TESs coated with a nanoporous layer of aluminium oxide resulted in a significant reduction of neointimal thickness (NIT) by 50% with a total dose of 60 μg of tacrolimus and 56% for a dose of 120 μg of tacrolimus, when compared with BMS. In the in vivo study by Kollum et al.28 using a swine model of restenosis, TES (JOMED, Rangendingen, Germany) with a nanoporous ceramic aluminium

<table>
<thead>
<tr>
<th>Variables</th>
<th>In-stent</th>
<th>In-segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference vessel diameter (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After procedure 2.94 ± 0.41 2.90 ± 0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 months 2.57 ± 0.48 2.57 ± 0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal luminal diameter (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After procedure 2.57 ± 0.36 2.27 ± 0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 months 1.58 ± 0.63 1.55 ± 0.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value  &lt;0.0001  &lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late loss (mm) 0.99 ± 0.46 0.72 ± 0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After procedure 12.50 ± 5.73 21.54 ± 8.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 months 38.66 ± 20.79 40.00 ± 20.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value  &lt;0.0001  &lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binary restenosis rate at 4 months* (%)</td>
<td>26.7</td>
<td>26.7</td>
</tr>
</tbody>
</table>

*Binary restenosis was calculated based on the unmatched data.

Table 3 Angiographic parameters related to acute stent recoil assessment (n = 40)

| Variables                                      |            |
| Mean diameter of balloon at the highest pressure (mm) | 3.17 ± 0.32 |
| Mean diameter of stent immediately after balloon inflation (mm) | 2.95 ± 0.37 |
| Acute absolute recoil (mm)                      | 0.22 ± 0.20 |
| Acute per cent recoil (%)                       | 7.11 ± 6.18 |

Figure 3 Cumulative frequency distribution curves of % minimal luminal diameter at pre-procedure, post-procedure, and follow-up.
oxide coating at a dose of 180 μg demonstrated a significant inhibitory effect on neointimal proliferation. However, the inhibitory effect on restenosis was counteracted by inflammatory reaction due to major particle debris as a result of cracking of the ceramic coating.

After these preclinical studies, two clinical trials were performed using a TES with a biocompatible and non-thrombogenic carbofilm™ coating (Janus; Sorin Biomedica Cardio, Italy). In the

---

**Table 4** Intravascular ultrasound measurements in matched pairs at post-procedural and 4 months follow-up (n = 42)

<table>
<thead>
<tr>
<th>Event</th>
<th>Post</th>
<th>Follow-up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel volume (mm³) (mean ± SD)</td>
<td>350.1 ± 170.7</td>
<td>377.2 ± 175.9</td>
<td>0.0002</td>
</tr>
<tr>
<td>Stent volume (mm³) (mean ± SD)</td>
<td>188.6 ± 98.7</td>
<td>190.7 ± 100.7</td>
<td>0.316</td>
</tr>
<tr>
<td>Luminal volume (mm³) (mean ± SD)</td>
<td>187.4 ± 93.4</td>
<td>123.5 ± 67.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plaque volume behind stents (mm³) (mean ± SD)</td>
<td>165.1 ± 75.9</td>
<td>186.4 ± 81.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intimal hyperplasia volume (mm³) (mean ± SD)</td>
<td></td>
<td>67.23 ± 48.36</td>
<td></td>
</tr>
<tr>
<td>In-stent volume obstruction (%) (mean ± SD)</td>
<td></td>
<td>34.78 ± 15.76</td>
<td></td>
</tr>
</tbody>
</table>

| Frequency of ISA (%)a                       | 34.8        | 21.4        |         |
| Resolved ISA at follow-up [n (%)]          | 10 (50)     | 7 (35)      |         |
| Persisting ISA at follow-up [n (%)]        | 3 (15)      |             |         |
| Late acquired ISA at follow-up [n (%)]     |             |             |         |
| ISA volume (mm³) [median (inter-quartile range)] | 2.69 (2.12–7.03) | 3.99 (1.88–7.39) |         |

SD, standard deviation; ISA, incomplete stent apposition.

*aFrequency of ISA was calculated as number of patients with at least one strut with incomplete stent apposition divided by the total number of patients.

---

**Table 5** Adverse cardiac events at 6 months (per-patient analysis)

<table>
<thead>
<tr>
<th>Event</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td>Target vessel</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td>Non-target vessel</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac death, stroke, or myocardial infarction</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td>Repeat PCI–ID-TLR¹</td>
<td>11</td>
<td>23.4</td>
</tr>
<tr>
<td>Repeat PCI–non-ID-TLR¹</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Repeat PCI–TVR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MACE (cardiac death, target-vessel myocardial infarction, or ID-TLR)</td>
<td>11</td>
<td>23.4</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>1</td>
<td>2.1</td>
</tr>
</tbody>
</table>

MACE, major adverse cardiac events; ID-TLR, ischaemia-driven target lesion revascularization; Non-ID-TLR, non-ischaemia-driven target lesion revascularization; TVR, target vessel revascularization; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

¹One patient experienced ID-TLR twice, but counted as one.

²One patient experienced both ID-TLR and non-ID-TLR.

---

‘FIM’ study using the Janus stent loaded with a 1.5 μg/mm² of tacrolimus, TES was associated with a 3.8% binary restenosis rate at the 6-month follow-up in non-diabetics and 16.9% in diabetics.29 After increasing the dose of TES from 1.5 to 2.3 μg/mm², the investigators performed a randomized trial including 332 patients to compare the performance of the TES with that of the BMS. The free drug—not incorporated in polymer or excipient—was released from wells carved in the abluminal side of the stent. No differences in angiographic results were observed at 6-month (in-stent late luminal loss; TES 0.65 ± 0.47 vs. BMS 0.66 ± 0.53 mm), and the 12-month MACE rates of TES were not lower than BMS (19.5 vs. 16.1%).30

The MAHOROBA strut has its own design with no previous clinical use and its mechanical performances were evaluated in this FIM study. Acute recoil analysis by QCA suggests that the MAHOROBA stent may have a relatively weaker radial strength than contemporary metallic DESs; the absolute recoil of MAHOROBA was 0.22 ± 0.20 mm, whereas % relative recoil was 7.11 ± 6.18%. Different methodologies of recoil assessment render comparison between different stents difficult. However, recent analysis by an independent clinical research organization (Cardialysis B.V.) provides us with comparative recoil analysis of a CoCr everolimus-eluting stent and the MAHOROBA stent employing the same methodology. According to the results, the acute recoil of the MAHOROBA seems to be higher, although stent oversizing can affect the results.15

The MAHOROBA stent is characterized by a biodegradable polyactic-co-glycolic acid coating with a bioabsorption time of about 6 months, resulting in a long-term sustained release of the drug. Although the MAHOROBA stent was used in patients with favourable characteristics and simple lesion, angiographic follow-up at 4 months demonstrated a mean in-stent late loss of 0.99 mm, which is equivalent or even slightly higher than the late loss observed in historical series with BMSs.

The reason for the absence of neointimal inhibition in MAHOROBA may be multifactorial: first of all, contrary to the mode of action of sirolimus and its analogues that inhibit mTOR and subsequently up-regulate p27, tacrolimus acts through different
pathways and involves the calcineurin–calmodulin complex. Therefore, its mode of inhibition of SMC proliferation is fundamentally different from sirolimus, and redundancy of signalling pathways for cell growth may supersede the specific inhibitory effect of tacrolimus. Pimecrolimus, a tacrolimus analogue might not only fail to inhibit but might also even promote further neointimal hyperplasia. In the recent prospective, three-arm, GENESIS study randomizing patients with de novo coronary artery disease either to paclitaxel-eluting (10 μg) or pimecrolimus/paclitaxel dual-eluting (162.5/10 μg) or pimecrolimus-eluting stent (325 μg), the pimecrolimus-eluting stent demonstrated the highest in-stent late loss (paclitaxel 0.58 ± 0.58 vs. paclitaxel/pimecrolimus 0.96 ± 0.73 vs. pimecrolimus 1.40 ± 0.67 mm) with the highest target vessel revascularization rate (2.0 vs. 14.4 vs. 35.0%) at 6-month.31 Therefore, the GENESIS study was suspended before complete enrolment was achieved. Taking these results into consideration, tacrolimus and its analogue might not be a suitable drug to prevent the restenosis even though efficacy in neointimal inhibition of neointima had been demonstrated in the animal studies. Secondly, the relatively low intra-parietal concentration during elution may be insufficient to effectively inhibit neointimal hyperplasia. Matter et al.11 demonstrated that in human saphenous vein cells, the IC50 of sirolimus to inhibit proliferation of vascular SMC was 4.1 × 10−9 mol/L, whereas the IC of tacrolimus was 0.38 × 10−6 mol/L. In the study by Mohacsi et al.,10 using human thoracic aorta, IC50 of sirolimus and tacrolimus was 1–10 × 10−9 and 1 × 10−6, respectively. These results suggest that a100- to 1000-fold higher tissue concentration of tacrolimus is necessary to exert the same neointimal inhibition as a SES. The MAHOROBA stent has a tissue concentration with a peak value of around 130 ng/mg artery (Figure 4), whereas Cypher is around 6 ng/mg artery,22 in animal models. The concentration of tacrolimus may therefore still be too low to achieve sufficient neointimal inhibition, although it is about 20 times higher than the SES. Recently, in a porcine coronary study, van Beusekom et al. assessed neointimal thickening after the implantation of a BMS, polymer-coated stent (Pol) without drug, a slow degrading low dose (1 μg/mm²) TES, and a fast degrading high-dose (2 μg/mm²) TES. The low-dose TES is similar to the MAHOROBA stent. Morphometry indicated that NIT in both TES was significantly reduced when compared with BMS and Pol up to 90 days (BMS: 335 ± 148; Pol: 381 ± 186; low-dose TES: 226 ± 52; and high-dose TES: 262 ± 80 μm). However, at 180 days, only the high-dose TES showed significantly lower NIT when compared with BMS or Pol stent because the slow degrading low-dose TES demonstrated catch-up of NIT between 90 and 180 days. Therefore, the inhibitory effect of low-dose TES (equal to MAHOROBA stent) on neointimal hyperplasia was somewhat suboptimal in the animal study, and high-dose TES might be optimal for DES. Thirdly, remnant polymer after complete elution of the drug could to some extent continue to stimulate neointimal growth in the stent. In a porcine model, the polymer of the MAHOROBA stent continues to be degraded up to 110 days but possibly without sufficient tacrolimus beyond 90 days to dampen the tissue response.30 Fourthly, the rate of incomplete stent apposition appears high at 35% in this study, although it is still in the range of previous study.33 The lack of proper elution of the drug at the abluminal side might be a potential explanation for the large presence of neointimal hyperplasia observed in this study.

Modification in the dose and release of tacrolimus might be mandatory to create an effective TES. Figure 4 shows the tissue concentration of tacrolimus in TES with different doses. Conversely, the MAHOROBA demonstrates the ability to maintain tissue concentrations for longer periods, but in the first 2 weeks is unable to attain sufficient concentration that are considered adequate for neointimal inhibition after stenting. Theoretically, a biphasic-release TES with a burst phase in the first 2 weeks followed by sustained release could have the ability to inhibit neointimal proliferation. A dual polymeric coating with rapid and slow drug-eluting profiles might be necessary to achieve biphasic release. An increased amount of polymer is indispensable to contain higher dose of drug than current, which could result in a thicker profile of the stent struts and a longer duration of absorption. It will be a technological challenge to develop a dual-coated stent with thin struts and an improved polymer degradation profile synchronized with drug release.

Intravascular ultrasound analysis in the current study demonstrated a significant increase in the plaque behind the stent (PBS) 4 months after the procedure. In the PISCES study using PESs with a durable PGLA polymer coating, specially designed for drug delivery with programmable pharmacokinetics, a significant increase in PBS at 4-month was reported in paclitaxel-loaded stents with equal or longer elution than 10 days, but not in-stents with a short elution of 5 days.34 These results suggest that the long-term presence of either drugs or PGLA polymer might cause extensive remodelling after stent implantation, presumably resulting from vessel inflammation. Also in the study using PESs, a significantly increased peri-stent area was observed at 6 months. However, sirolimus36 or everolimus-eluting stents26 with durable polymers, this effect on positive vascular remodelling has not been reported.

The current study has several limitations. The angiographic and IVUS follow-up were only performed at 4 months, which might be
too short to assess the full extent of neointimal hyperplasia after DES implantation. At the time of the study design, further invasive imaging with angiography and IVUS was planned in the protocol to 12 months to assess the full process of neointimal hyperplasia. However, after evidencing high amounts of neointimal hyperplasia with high rates of ischaemic TLR events at 4 months, the protocol was amended by the data safety monitoring board for safety reasons. It was decided to monitor patients more carefully with non-invasive stress ECG testing at 6 months and 9 months. Since the scientific goal had not been achieved, the invasive angiography originally planned at 12 months for scientific purposes was abandoned, and angiographic follow-up after 4 months was only performed for clinical reasons. Frequency of incomplete stent apposition was as high as 34.5%. The rate of malapposition, however, was calculated as the number of patients with at least one strut with incomplete stent apposition divided by the total number of patients and does not reflect the number of malapposed struts or the malapposed volume. This study did not mandate IVUS-guided stenting, so that post-dilation was completely left to the operators’ discretion. In addition, given the relatively high stent malapposition rate and % acute recoil, it is difficult to know how much each component of the stent (i.e. polymer, stent platform and drug) could contribute to the failure of this DES.

Despite the conceptual advantages of using tacrolimus with a biodegradable polymer, this FIM study has failed to establish the effectiveness of this stent. Taking the multifactorial reasons of failure into consideration, tacrolimus formulation of the current stent seems unsuitable to prevent restenosis. Technical improvements enable us to construct TES with a higher drug content and improved polymer degradation profile in synchronization with drug release.

**Funding**

The study was sponsored by Kaneka (Osaka, Japan).

**Conflict of interest:** T.N. is an employee of Kaneka corporation.

**References**


**Different focal delayed gadolinium-enhancement patterns using cardiac magnetic resonance in a case of diffuse giant cell myocarditis**

Arshid Azarine1,*, Romain Guillemain2, and Patrick Bruneval3

1Department of Cardio-Vascular Radiology, Hôpital Européen Georges Pompidou, 20-21 rue Leblanc, Paris 75015, France; 2Thoracic Transplant Unit, Hôpital Européen Georges Pompidou, 20-21 rue Leblanc, Paris 75015, France; and 3Department of Pathology, Hôpital Européen Georges Pompidou, 20-21 rue Leblanc, Paris 75015, France

*Corresponding author. Fax: +33 156 092 311, Email: azarine@free.fr

A 17-year-old man was admitted for new onset of fatigue with dyspnoea. He did not present fever or a recent history of flu-like symptoms. The results of the physical examination and ECG were unremarkable except for a sinus tachycardia at 116 b.p.m. Echocardiography demonstrated severe global hypokinesia of both ventricles with left ventricular ejection fraction (LVEF) of 10%. Laboratory tests revealed a troponin I level of 0.02 ng/mL (normal <0.015 ng/mL), C-reactive protein of 57 mg/L (normal <10 mg/L), creatine kinase of 54 UI/L (normal <145 UI/L). Cardiac magnetic resonance (CMR) confirmed severe global dysfunction of both ventricles with LVEF of 12% and RVEF of 10%. Gadolinium delayed enhancement (DE) imaging demonstrated three different types of focal linear DE: mid wall and sub-endocardial ‘right-sided’ DE of the septum (black arrow), sub-epicardial DE of the lateral wall (white arrow) and sub-endocardial ‘ischaemic-like’ DE of the lateral-basal wall (Panel A, short-axis view, Panel B, four-chamber view, LV: left ventricle). The patient condition worsened rapidly and he underwent emergency heart transplantation. Pathology of the explanted heart revealed a diffuse giant cell myocarditis (GCM) occurring predominantly in the delayed enhanced areas as demonstrated by CMR (haematoxylin–eosin-stained specimen, original ×40; Panel C, septal specimen; Panel D, lateral LV wall specimen). Higher magnification of the most infiltrated areas demonstrated focal of dense lymphocytic infiltrates with numerous giant cells without evidence of ischaemic myocardial injury, particularly, in the endocardial area of the lateral basal wall (haematoxylin–eosin stain, original ×400, Panel E, midwall area of the septum; Panel F, endocardial area of the lateral basal wall). A 2 year follow-up by routine endomyocardial biopsy has shown no recurrence of GCM or rejection. On these DE images, the signal of the diffusely infiltrated myocardium by GCM was null, the different patterns of focal hyper-enhanced areas being relevant for the most infiltrated areas when compared with histology.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2009. For permissions please email: journals.permissions@oxfordjournals.org.