The Biotronik Bioabsorbable Magnesium Scaffold DREAMS

Ron Waksman, MD, FACC, FSCAI
Professor of Medicine (Cardiology) Georgetown University,
Associate Director Division of Cardiology
Washington Hospital Center Washington DC
Disclosures

- Consultant: Biotronik, Medtronic, Boston Scientific. Abbott Vascular
- Speaker: Biotronik BSC, Medtronic, Abbott Vascular
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A scaffold is different from a stent

<table>
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<th>Drug Eluting Scaffold</th>
<th>Drug Eluting Stent</th>
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<td>Temporary backbone</td>
<td>Permanent backbone</td>
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<tr>
<td>Degradable polymer coating</td>
<td>Permanent polymer coating</td>
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<td>After elution period of about 3 months, the drug is completely gone</td>
<td>Elution time over 2 months, with possible remaining drug embedded in permanent polymers</td>
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- The mechanism of a temporary scaffold is different from a permanent stent.
- It fulfills a transient role in supporting the vessel and eluting a drug to inhibit neointimal hyperplasia.
- Permanent caging of the vessel is eliminated.
- After scaffold degradation, the vessel is returned to its natural functionality – no polymer or drug is left behind to cause inflammation.
Challenges With Bioabsorbable Stents

- Time of degradation
- Rate of degradation
- Biodegradable products
- Remaining polymer
- Biocompatibility
- Elution of the drug from biodegradable stents
- Scaffolding and radial force
- Recoil: early and late
- Radiopacity of the stents
AMS is a metallic stent with favorable mechanical properties

• Design & Manufacturing
  • Based on Finite Element Analysis
  • Laser cut and polished surface

• Mechanical parameters
  • Low bending stiffness
  • Low crossing profile (1.2 mm)
  • Low recoil (<5%)
  • High radial strength (~1 bar)

• Clinical effects
  • Good trackability and device success rate of 99.4%*
  • Good stent apposition

* Analysis includes existing AMS-1 clinical data (BEST-BTK, INSIGHT, PROGRESS)
Analysis of degradation products by EDX analysis

Mg alloy before degradation

Conversion layer: soft shell of \( \text{Ca}(\text{PO}_4)_2 \)

Mg alloy after 13 days in porcine blood

28 days in mini-pig
Acute mechanical properties of Mg alloys more favorable than that of polymers

**Stress-Strain-Diagram**

**Collapse pressure**

Theoretical strut section to obtain similar mechanical results:

- 316L stent
- Mg stent
- PLA stent

DREAMS: ~120µm

BVS: ~150µm
Degradation product composition in vivo

- Magnesium of the AMS scaffold is completely replaced with conversion products
- The polymeric drug coating is fully degraded
- Degradation process and conversion product composition in clinical and preclinical use is similar

Sources: J. Riedmüller; Yucatan Minipig, 42 days FUP // Zartner P. First Successful Implantation of a Biodegradable Metal Stent Into the Left Pulmonary Artery of a Preterm Baby. Catheterization and Cardiovascular Interventions 66:590–594 (2005)
AMS allows non-invasive imaging of the stented vessel

IVUS/OCT
stent visibility

MRI

16 MSCT

MRI/MSCT
- No stent artefact
- Optimal vessel lumen imaging

Source: Erbel et al, Herz 32 · 2007 · Nr. 4
Previous bare AMS devices demonstrated safety, but...

- Perfect ingrowth of AMS
- Safe in human coronary and peripheral arteries (150 patients)
  - No death, no MI, no scaffold thrombosis, no distal embolization, no excessive inflammation
  - Device success rate of 99.4%
- Absorbed as intended in several months
- Fully CT/MRI compatible

Source: Courtesy Dr Di Mario: PROGRESS AMS-1, long term results (15 months) showed perfect ingrowth
AUS 004-001

Post Implantation

4 Months

16 Months
Intracoronary ISDN induced vasodilatation in Permanent Metal Stent (PMS) control patients and Absorbable Metal Stent (AMS) patients within stent and in proximal reference segments at 4 months post implant. 

Courtesy of Dr Miles Dalby Royal Brompton & Harefield
... failed to show sufficient efficacy

Two main drivers for restenosis

Post implantation

Degradation

4 month follow-up

Contribution to lumen loss

Loss of stent scaffolding

In-stent neointima

53%

47%

Prolongation of stent scaffolding should reduce restenosis rate (ischemic driven TLR of 23.8% for AMS-1)

Source: PROGRESS AMS-1 IVUS
DREAMS is based on a proprietary magnesium technology

For coronary scaffolds, tailor-made magnesium alloys provide the best balance between biocompatibility, mechanical properties and absorption characteristics.
DREAMS evolves as a new therapy concept and addresses the two main limitations of bare magnesium scaffolds

**Platform development**
- **AMS-1**
  - 4-crown design

**Enhanced platform** with prolonged stability
- Refined alloy providing 2-3 times slower degradation
- Approximately 30% thinner struts

**Drug Elution**
- **DREAMS**
  - AMS-2 platform
  - Degradable polymer
  - Paclitaxel elution

**First generation device**
- 4-crown design
Why Paclitaxel...

- More than 5 million Paclitaxel eluting stents implanted
- More than 15 clinical trials with Paclitaxel eluting stents demonstrating safety & efficacy
- The only drug working in DEB and showing convincing results
- Very stable in combination with magnesium
- Allows safe degradation and inhibition of NIH
DREAMS, the **DRug Eluting Absorbable Metal Scaffold** is fully degradable.

**Drug carrier**
- Fast degrading polymer

**Backbone**
- Customized Mg-alloy
- Good biocompatibility

**Drug**
- Antiproliferative paclitaxel

**Delivery system**
- Modified PRO-Kinetic

**Sizes used in FIM**
- 3.25/3.5 x 16
- 6F compatibility
DREAMS provides scaffolding and paclitaxel release up to 3 months

- Mg degradation (conversion)
- Stable drug carrier layer
- Diffusion controlled drug release

- Mg degradation completed
- Drug release completed
- Degradation of polymer

- Drug carrier layer degradation completed
- Beginning disintegration of Mg degradation product

Source: preclinical studies, data on file
First generation DREAMS shows in vitro elution behavior comparable with Taxus

- High stability of paclitaxel allows to control processes in this system comprising a degradable backbone and a degradable drug carrier
- Based on preclinical tests, elution time in-vivo elution is estimated at 3 months

Source: in vitro measurements, data on file
DREAMS shows low inflammation scores - comparable to Taxus

- Comparison between DREAMS and Taxus Liberté control shows low inflammation scores at 28, 90 and 180 days
- Minor increase of inflammation at 28 days seen in the DREAMS arm due to degradation of base materials

Source: AccelLAB preclinical studies, data on file
DREAMS late lumen loss is comparable to Taxus

Late Lumen Loss [28/60/90/180d]
QCA, Median Values

Source: AccelLAB preclinical studies, data on file
Histological Images at 28 days show fast healing of DREAMS

Source: AccelLAB preclinical studies, data on file
All photos same magnitude and scale
Histological Images at 90 days show nearly complete healing in DREAMS group

*DREAMS vessels are smaller than actual due to shrinkage during tissue processing (no scaffolding as in reference group)

Source: AccelLAB preclinical studies, data on file
All photos same magnitude and scale
At 180 days there is no catch-up after complete drug release of DREAMS

Black spots above represent Mg degradation product (amorphous Calcium phosphate phase)

Source: AccelLAB preclinical studies, data on file
All photos same magnitude and scale
BIOSOLVE-I: 47 patients enrolled in 6 centers
Angiography Follow-up will be completed in 2011

Study Design

DESIGN: Prospective, multi-centre, first in man trial

PRINCIPAL INVESTIGATOR:
J. Koolen, Eindhoven, The Netherlands

PRIMARY ENDPOINT: TLF* at 6 months (cohort 1) and 12 months (cohort 2)

PARTICIPATION CENTERS:
Belgium: S. Verheye, Antwerpen
Germany: R. Erbel, Essen, M. Haude, Neuss, C. Hehrlein, Freiburg
Switzerland: P. Erne, Luzern

Up to 50 patients (FPI 27 July 2010) in 6 clinical sites in Belgium, Germany, the Netherlands and Switzerland

Cohort 1
Clinical follow-up at 1 month
QCA & IVUS follow-up at 6 months**

Cohort 2
Clinical follow-up at 1 month
QCA, IVUS, OCT follow-up at 12 months

Clinical follow-up at 24 & 36 months

* Composite of cardiac death, myocardial infarction and clinically driven TLR. ** optional vasomotion testing
Case 01
COURTESY OF Dr Haude Biosolve 1 PI
Case 02
Conclusions

• The development of metallic bioabsorbable scaffolding is challenging
• The stents struts are thicker when compared to metallic durable stents
• Radial force issues could lead to immediate and early recoil
• Drug elution is mandatory to inhibit neointima proliferation
• Harmonization of the degradation of the alloy the biodegradable carrier and the drug are essential for a successful program