In BioMime™, the polarized triad of DES design is taken care of!

The resultant stent blends the safety of a BMS with efficacy of a DES

SEM pictures of BioMime™ endothealization in porcine coronary artery at 30 days.

In a preliminary Safety and Efficacy Single Centre Clinical Trial, BioMime™ demonstrated 0% MACE at 6 months.

Dear Doctor,

Welcome to the first edition of Vascular Voyage – A quarterly update on vascular interventions.

From the time Grossmann and others triggered this zeal in treatment of obstructive vascular disease via minimally invasive technique, the field of endovascular interventions has attracted the best brains to apply concepts in engineering, material science, polymer technology, pharmaceutical sciences and bio-technology to bring rapid yet clinically relevant changes in order to alleviate human suffering.

We are now witnessing changes in the field of vascular interventions which are propelled not just by the general enthusiastic flavor of development in science and technology but also by this primal need to surpass disease and perhaps even delay death!

In this regards, Meril Life Sciences comes as a new kid on the block, which like the metaphorical kid described by Sir Isaac Newton, is in the business of discovering that ‘new shell or pebble from the vast ocean of truth’ that lays all undiscovered before us.

Asimov’s 1960’s thriller ‘Fantastic Voyage’ has inspired and intrigued the lovers of vascular interventions. Riding the ‘Proteus’ to treat a disease from inside has perhaps been a secret fantasy of every individual connected to this field. Your copy of Vascular Voyage comes as a quarterly communication, written with an objective to disburse scientific information not just on developments taking place in Meril’s own research stable, but also on best practices in the field of Endovascular interventions – Coronary, Peripheral, Neurovascular and Structural Heart disease.

The readers will have the pleasure of being face-to-face with the Grants and Coras of this world as they share from the distillate of their acquired wisdom in day-to-day clinical practice. The contents will include – latest in vascular interventions, current treatment trends, difficult case of the quarter, complications and how to avoid them and a special feature pertaining to ‘day-in-the-life-of…’ well, some of you!

Vascular Voyage will be available both in print (distributed by our channel partners) and on-line as a downloadable pdf version from our website www.merilife.com. This issue discusses the clinical need and the development of a novel sirolimus eluting coronary stent from Meril Life Sciences, we hope you will enjoy the read. Do send in your feed back at vascularvoyage@merilife.com.

Happy readings and best regards,

Team Meril Life Sciences

NEWER CONCEPTS IN STENT DESIGN & DEVELOPMENT OF A NOVEL SES

The Penrose’s triangle of DES development

The criteria of DES safety over the past 7 years of their existence have emerged as their ability to reduce vessel injury, ensuring complete stent apposition, involving the use of thrombo-resistant polymers, ensuring optimal anti-platelet treatment for reduction of acute events and encouraging re-endothelialization. Resolving local inflammation and finally facilitating generation of functional endothelium account for reduction of late events.

Considering the above safety parameters, criteria for sound DES construction can be listed as:

A thin strut stent platform design

- that minimizes injury
- ensures complete apposition
- endothelializes well due to conformability against the vessel wall

A drug that ensures anti-proliferative/anti-inflammatory effect

- is not cytotoxic
- has a broad therapeutic window
- has been tested in similar clinical situations

A polymeric coating

- is non-thrombogenic
- has elastic properties to allow for thin coating and to withstand mechanical trauma
- is biodegradable

Having identified the classical triad of an ‘ideal DES’ construction, the challenge of creating one is like creation of the Penrose’s impossible triangle.

The Penrose’s triangle (Fig. 1) is a typical combination of properties which cannot be realized by any 3-dimensional object in ordinary Euclidean space and is a demonstration of the current challenges during design and development of an ideal DES. All the classical parameters of DES construction are polarized and offer little homogeneity when put together.

Any compromise in the stent architecture and the drug formulation would lead to incomplete healing, likewise inappropriate polymer usage would cause inflammation and the formulation itself can lend sub-optimal drug release kinetics.

Moving towards biomimicry and development of BioMime™ Sirolimus Eluting Coronary Stent System

Derived from the clinical and the technological need gaps in the existing coronary stents and DES, the BioMime™ Sirolimus Eluting Coronary Stent System has been developed on simple yet fundamentally sound principles. The resultant DES has the ability to be arterially biocompatible leading to its predictably safe and efficacious profile.

BioMime™ Sirolimus Eluting Stent (SES) – Primary Device Description

The BioMime™ SES is made of following three components:

- Stent = NeXgen™ Cobalt Chromium Coronary Stent System
- Drug = Sirolimus (1.25 μg/mm² of stent surface)
- Polymer = BioPoli™ the biodegradable co-polymer combination of Poly-L-Lactic Acid (PLLA) and Poly-L-Glycolic Acid (PLGA)
The Right Stent Architecture

The BioMime™ SES (Fig. 2) employs the CE marked NexGen™ Cobalt Chromium Coronary Stent System—a novel concept conceived to minimize intra-aortic injury.

The design stretches the boundaries of structural engineering with ultra-low strut thickness stent (65 μm maintained across all dimensions) without any loss in radial strength. On bench testing, NexGen™ demonstrates a high radial strength with a mean recoil of <3% and a foreshortening of 0.29%.²

The novel stent design ensures a morphology mediated expansion³ (Fig. 3) due to a hybrid cell design structure (open cell configurations in the centre and closed at the edges). This unique method of expansion eliminates the classical dog-boning seen in conventional designs and also ensures minimal edge injury⁴.

Further the struts have unique strut width variability (Fig. 4) which ensures flexibility while retaining high radial strength.

Evidently due to these features the stent demonstrates superior acute gain and complete wall apposition (Fig. 5), and thus appears to endothelialize quickly (Fig. 6) in porcine coronary artery model at 28 days⁵.

The stent delivery system also ensures minimal arterial injury. The semi-compliant rapid exchange balloon catheter shoulders are carefully constructed short taper and abrupt with a marginal over-hang (Fig. 7). This allows for high trackability and deliverability at the same time minimizing any chance of balloon related edge injury⁶.

In an interesting pre-clinical evaluation work undertaken in porcine coronary artery model, low strut thickness (65 μm) NexGen™ stents were compared versus high strut thickness (91 μm) Driver stent (Medtronic, USA). Piglets were sacrificed at 28 and 90 days to appraise the biocompatibility. The primary endpoint was mid-in-stent neo-intimal thickness. Histomorphometric analysis at 28 days showed significant differences in mid-stent neo-intimal thickness (0.18 ± 0.08 mm for NexGen™ segments versus 0.30 ± 0.41 mm for Driver segments, p = 0.03) favoring thinner strut cobalt chromium stents. (Fig. 8)

This study corroborates with earlier stated superior results obtained by low strut thickness stents in humans by Kastrati et al which allows for predictability in lowering restenosis and TVR incidence versus high strut thickness.

The Right Anti-proliferative Drug—Sirolimus

BioMime™ stent releases the tried and tested Sirolimus. In this context; Sirolimus is the right candidate for DES application since it targets the “final common pathway” to prevent vascular smooth muscle cell proliferation.

The efficacy of Sirolimus eluting stents in animals has long been established and a large volume of published data in human coronaries is available.

At both 28 and 90 days, BioMime™ stented segments appear to be as safe as corresponding control stents or Cypher while demonstrating a superior trend in reducing neo-intimal thickness as compared to either the control stent or Cypher⁷.

The control stent which was NexGen™ coated with biodegradable polymer was found to be equivalent in terms of biocompatibility to NexGen™ bare stent itself suggestive of non-inflammatory nature of the polymer⁸.

BioPoly™ is a biodegradable polymeric base in BioMime™ comprising of a proprietary co-polymer formulation mix consisting of Poly-L-Lactide (PLLA) and Poly-L-α-Glycolide (PLGA). The principle mode of degradation of BioPoly™ is via hydrolysis. Degradation first proceeds by diffusion of water into the material, followed by random hydrolysis; fragmentation of the material and finally a more extensive hydrolysis accompanied by phagocytosis, diffusion and metabolism.
Once hydrolysed, the products are either metabolized or excreted. The lactic acid thus generated becomes incorporated into the tricarboxylic acid cycle (Kreb's cycle) and is excreted as carbon dioxide and water.

BioPoly™ has been found to have a short degradation time and has been tested non-inflammatory in the preclinical model. The composition offers a uniform stent coating and does not crack, web, lump or stick to the balloon surface.

On BioMim™ the drug plus BioPoly™ coating thickness is maintained at 2 μm which is lowest amongst the available DES on the market (Fig. 10).

Achieving biomimicry behaviour - Endothelialization

BioMim™ in pre-clinical model

In pre-clinical model, BioMim™ demonstrates almost 100% endothelialization at the end of one month as is noticed from the SEM picture here. A uniform endothelial coating over and between the struts on edges (closed cell configuration) and in mid-segment (open cell configuration) is observed (Fig. 11).

BioMim™ Clinical Update

Based on the encouraging pre-clinical results and predictable design configuration, BioMim™ was studied in a phase IV prospective, single arm, primary efficacy and safety study involving 30 patients. All patients represented with a single, discrete de novo lesion and were stented with BioMim™ ranging from diameters 2.5–3.5 mm and lengths from 13 to 24 mm. Primary endpoint was MACE defined as death, myocardial infarction (MI) or any ischaemia driven target lesion revascularization (TLR).

100% patients were discharged without any pre, peri or post procedural complication. Zero percent MACE was noted at six months clinical follow-up. No case of death – cardiac or non-cardiac, no MI (Q-wave or non-Q-wave), no ischemia driven TLR was reported.

All the patients will now be entering 8 months angiographic and IVUS follow-up to understand the stent’s Qualitative Coronary Angiography (QCA) parameters of late lumen loss and volumetric obstruction.

RAVEL study reported a MACE of 5.8% in Cypher arm at 1 year follow-up and so far with zero percent MACE in BioMim™ stented patients the results are encouraging.

In a larger multi-centric, non-randomized all comers trial known as BioMim 1 trial, BioMim™ is being studied in 250 patients present in a real world scenario and the only exclusion criteria are Saphenous vein grafts (SVGs), Acute Myocardial Infarction (AMI), left main disease and a Left Ventricular Ejection Fraction (LVEF) of <30%.

Follow-up schedule is to be maintained at 30 days, 6 months, 1 year and then annually up to 5 years. All patients will undergo angiographic follow-up every 8 months.

Primary safety and efficacy endpoints are defined as MACE which is a composite of death, MI (Q-wave and non-Q-wave), emergent CABG and clinically driven TLR. In-stent and in-segment late loss will be calculated via QCA. Secondary end-points will be MACE at 1 year and device related serious adverse events until 12 months, angiographic stent thrombosis (acute, sub-acute and late). Angiographic and device success and procedural success will be additional parameters in the secondary point.

Currently the trial is underway and no untoward feedback related to device usage has been reported so far.

Insights and Conclusions

The first generations DES were laced with late stent thrombosis and were created on bulky stent platforms with questionable deliverability and polymer biocompatibility. BioMim™ Sirolimus Eluting stent comes as a fresh approach in designing of DES, keeping in mind that eventually the DES should endothelialize in a few months.

Hence all the ingredients that allow for optimal endothelialization have been incorporated in BioMim™ development.

The stent used is CE marked cobalt chromium, ultra-low strut thickness (65 μm) with variable strut width and a novel geometry involving an intelligent hybrid of open and closed cells which allows for morphology mediated expanded of the stent while retaining high radial strength and conformability.

The drug employed is Sirolimus which is an ideal choice considering that it acts on the common final pathway of cell division cycle without exceptional risk of necrosis induction.

The BioPoly™ is a co-polymer formulation of well known biodegradable polymers (PLLA and PLGA) which are non-inflammatory and allow for a 2 μm stable coating.

The resultant SES has drug elution kinetics of 30 days and a polymer degradation which is short and well documented.

BioMim™ has been found to be safe and efficacious in pre-clinical models and in the primary safety and efficacy study. Notable at 6 months is the zero percent MACE. Data from the large multi-centric trial involving 250 real world patients will further establish its credibility in routine clinical practice.

Hence based on the available, pre-clinical and initial clinical reports, it can be predicted that this 3rd generation DES has adapted itself from the learning curve of the past DES and will rightfully set path for the biomimicry concept in DES design for future.

References

5. Primary safety and efficacy data in 30 patients. Dr. Sameer Dani presented during India LVE 2010, New Delhi, India. Unpublished data.
7. The BioMim 1 data – real world application of BioMim™ a multi-center trial. Dr. Ashok Seth’s presentation during India LVE 2010, New Delhi, India. Unpublished data.