Evaluation of second generation DES in an ex vivo model of stent thrombosis

Alexander Sheehy1, Leigh B Kleiner1, Stephen Pacecti1, Syed Hassainy2, Mikhail Trollsas1, Stuart K Williams1
1R&D, Abbott Vascular, Santa Clara, CA; 2University of Louisville, Louisville, KY

Background: Thrombosis remains a risk following all types of endovascular intervention. Though considerable advances have been made in stent design, the design factors leading to stent thrombosis—stent design, drug elution, and coatings—continue to improve and are not completely understood. It is believed that surface thrombogenicity can be reduced by the incidence of device-induced vessel thrombosis.

Methods: The left and right femoral artery of five domestic Yorkshire swine were cannulated to create an ex vivo blood shunt through polyethylene tubing with silicon coated tubing and low flow deployment to the femoral artery to the femoral vein. 30x18mm stents in the following groups were evaluated: bare metal stent (BMS, ML VISION®), collagen coated BMS (BMS-c), XIENCE V® (XV), and Endeavor Resolute (Res), and uncoated silicone tubing (negative control). Six stents from each group were included into the ex vivo shunt system randomized in sequence. No anticoagulation or antiplatelet agents were administered to the animal. Blood was allowed to circulate through the shunt for 30 minutes, following which stents were weighted for gravimetric assessment of thrombus burden and images were obtained.

Results: As expected, positive control collagen coated BMS exhibited the greatest amount of thrombus, followed by BMS, then Endeavor Resolute. Xience V and uncoated silicone tubing had the least thrombus. The pre-stenting to post-stenting weight differential of each was—BMS: 0.06±0.04, BMS-c: 0.10±0.02, Res: 0.02±0.003 (p<0.05 vs BMS, BMS-c, XV); 0.01±0.007 (p<0.05 vs BMS, BMS-c, Res), Silicone tube: 0.010±0.011 (p<0.05 vs BMS, BMS-c, Res).

Conclusion: In a model of acute thrombogenicity, Xience V demonstrated the least amount of thrombus in comparison to other second generation DES and BMS. This preclinical thrombogenicity data appears to corroborate the low acute thrombosis rates observed with Xience V in clinical practice.

Microarray Analysis for Nobori Biolimus A9 Eluting Stent and Xience V

Evolisus Eluting Stent in Porcine Coronary Artery

Arshio Sumida, Selvamuthu Natarajan, Deepal Panchal, Jinsheng Li, Dongming Hou, Nicholas Chronos, Jai Pal Singh, Surendra Chavan, St Joseph’s Translational Research Institute, Atlanta, GA

Background: Drug eluting stents (DES) have decreased the rate of in-stent restenosis and been used as one of the most important devices for treatment of coronary artery disease. Although most drugs inhibit mammalian target of rapamycin (mTOR), the biological effects of DES toward stented vessels remain unknown. We examined transcript expression by microarray analysis in stented blood vessels implanted with two types of new generation DES, Nobori and Xience V.

Methods: One month after stent implantation in porcine coronary arteries, all animals were euthanized and stented arteries were harvested for a microarray analysis. In this study, total RNA from stented vessel segments (Nobori: n=4, Xience V: n=3) or non-stented vessel segments (Control: n=2) were evaluated by using Agilent array genes. Significant genes were selected with a cutoff of p<0.05 and fold change ≥2.

Results: 3,239 of 40,424 genes were considered differentially expressed and 533 genes were exclusively altered in each group. In stented vessel segments (Control: n=2) were evaluated by using Agilent gene arrays. Significant genes were selected with a cutoff of p<0.05 and fold change ≥2.

Conclusion: Based on this preliminary microarray gene expression study, expression of inflammatory cytokines and adhesion molecules involved in inflammatory and immune reactions were downregulated in Nobori stented blood vessels compared to Xience V.

Evaluation of Drug Tissue Concentration Following Stenting in a Healthy Rabbit Iliac Model

Alexander Sheehy1, Saami K Yazdani1, Ed Berger1, Rosy S Donn2, Tu D Ngo2, Stephen Pacecti1, Syed Hassainy1, Frank D Kolodejch2, Renu Verma1
1R&D, Abbott Vascular, Santa Clara, CA; 2CYPath, Inc, Gaithersburg, MD

Background: Drug eluting stents (DES) have significantly improved restenosis rates. However, some DES have been shown to inhibit wound healing and re-endothelialization, leading to an increased risk of late stent thrombosis (LST). Prolonged drug tissue concentration has been implicated as a potential source of delayed healing. Although in vitro models can assess the dose and time-dependent release kinetics of DES, in vivo models are needed to provide a more clinically relevant environment for drug tissue content. The purpose of this study was to assess the tissue drug concentrations of stented iliac rabbit arteries for four different DES on a head-to-head basis.

Methods: Four DES were evaluated: Cypher (SES, sirolimus), Endeavor Sprint (ZES-S, Zotarolimus), Endeavor Resolute (ZES-R, Zotarolimus), and XIENCE V® (EES, Everolimus). Stents were implanted into both healthy rabbit iliac arteries for durations of 3, 10, 28, 42, and 90 days. Tissue drug concentrations were measured with liquid chromatography-mass spectrometry (LCMS).

Results: A model was created for tissue concentration based upon duration, treatment group, and interaction effects (p=0.01, r2=0.51). Both treatment and duration were significant. It is critical that tissue concentration (p<0.001). The drug tissue concentration curve for ZES-S was significantly higher at 3 days. At 90 days, tissue drug concentration for ZES-R was significantly higher than the other three devices (ng/mg): EES: 0.38±0.37, ZES-S: 1.25±0.83, SES: 1.27±0.52, ZES-R: 3.53±1.27. p<0.001 ZES-R vs SES and XES-R at 90 days. The tissue drug concentration for ZES-S was numerically higher than for EES, but not significantly so.

Conclusion: In a healthy rabbit iliac artery, tissue drug concentration following stenting was different between the different drug eluting stents as a function of time. Tissue drug concentration was greatest at early time points with ZES-S and at late time points with ZES-R. Differences in tissue drug concentration and duration of drug in tissue may have implications for DES efficacy and inhibition of healing.

Which Genes of the Nitric Oxide Pathway Contribute to Vascular Dysfunction Following DES Implantation in Swine Coronary Arteries?

Selvamuthu K Natarajan, Traci Goodchild, Surendra Chavan, Michael Sweet, Dongming Hou, Nicolas Chronos, Jai Pal Singh
Saint Joseph’s Translational Research Institute, Atlanta, GA

Background: Histological studies have shown that pig coronary arteries become endothelialized within 30 days after the implantation of drug eluting stent (DES). However, quantitative angiographic assessment shows vasoconstriction in response to acetylcholine challenge, indicating abnormal endothelial function. The present study was aimed to understand the molecular mechanism of endothelial dysfunction in DES implanted vessels.

Methods: Either bare metal or drug eluting stents with different polymers or drug were deployed in farm pigs in a total of 16 vessels. After 30 days, in vivo vascular function was assessed by acetylcholine challenge test. Vessels were harvested for histology, quantitative RT-PCR and western blot analysis. Specific analysis of nitric oxide pathway genes was performed.

Results: In vivo quantitative angiography confirmed vasoconstriction and vasodilatation indicating the presence of endothelial dysfunction in DES implanted arteries. Real-Time PCR showed a major upregulation of two of the NOS pathway genes, Arginine (100-3000 fold) and DDAH (5-7 fold). Only a small but significant (2 fold) change in eNOS gene expression was also observed. The gene expression changes were localized in the intima and media as the majority of the tissue used was derived from the intima and media. Histological evaluation showed higher angiogenesis in DES implanted vessels as compared to the BMS implanted arteries. Our results suggest that increase in expression of genes related to the angiogenic response whereas high arginine expression may deplete the substrate for NO generation and thereby contribute to endothelial dysfunction. An increased expression of DDAH is expected to be beneficial by reducing ADMA and superoxide generation.

Conclusion: Gene expression studies have provided new insight into the role of nitric oxide pathway genes in vascular response and endothelial dysfunction observed in DES implanted pig arteries. Our studies for the first time show that arginine and DDAH may be important players in modulating vascular response in DES implanted coronary arteries.

Pharmacokinetic Evaluation of Drug Eluting Stents in a Healthy and Atherosclerotic Rabbit Iliac Model

Alexander Sheehy1, Saami K Yazdani1, Ed Berger1, Rosy S Donn2, Tu D Ngo2, Stephen Pacecti1, Syed Hassainy1, Frank D Kolodejch2, Renu Verma1
1R&D, Abbott Vascular, Santa Clara, CA; 2CYPath, Inc, Gaithersburg, MD

Background: Though drug eluting stents (DES) have significantly improved restenosis rates, some (DES) have been shown to inhibit re-endothelialization, leading to an increased risk of late stent thrombosis. An optimal DES design would deliver sufficient drug to inhibit restenosis but have minimal impact on healing. Most pharmacokinetic (PK) studies have been performed in healthy animals and the relevance of this patients with atherosclerotic disease remains an open question. The purpose of this study was to assess the tissue drug concentrations achieved with several DES in both healthy and atherosclerotic rabbit iliac arteries.

Methods: Four DES were evaluated: Cypher (SES, sirolimus), Endeavor Sprint (ZES-S, Zotarolimus), Endeavor Resolute (ZES-R, Zotarolimus), and XIENCE V® (EES, Everolimus). Stents were implanted into both healthy and atherosclerotic rabbit iliac arteries for durations of 3, 10, 28, 42, and 90 days. Tissue drug concentrations were measured with liquid chromatography-mass spectrometry and compared between devices and models.

Results: A multivariate model is being assembled to determine the dependency on model type, treatment type and duration. At all time points and for all types of DES,