vessels, can lead to excessive proliferation. Transient systemic inactivation of monocytes and macrophages by iposomal alendronate reduced neointimal formation and restenosis in the stented hypercholesterolemic rabbit model in a manner that can be used independent of stent number, position, or overlap and with possible multiple dosing.

The Endothelial Nitric Oxide Synthase (GIu298Asp and -786T>C) Gene Polymorphisms Are Associated With Coronary In-Stent Restenosis

AbstractVolume Mohamed Ilyas, Charles Knight, Emma Hawe, Kim Pux, Steve Humphries, National Heart and Lung Institute and Royal Brompton Hospital, London, United Kingdom, British Heart Foundation Laboratories for Cardiovascular Genetic Studies, UCL Medical School, London, United Kingdom.

Background: Coronary stent deployment is a major advance in percutaneous treatment of ischemic heart disease, but 10-40% of patients still develop angiographic restenosis by 6 months due to neointimal hyperplasia. Partial gene polymorphisms, including genetic factors, can contribute this process. We have conducted a prospective study to examine the involvement of genetic risk factors (eNOS, ACE, MMP-3, IL-6, and PECAM-1) in restenosis following coronary stent deployment.

Methods: 226 patients who underwent elective coronary artery stenting to de novo lesions in native coronary arteries were studied. 205 (90.7%) patients were restudied by coronary angiogram at 6 months and the stented lesions were assessed with automated quantitative angiography system. Genotype was determined by PCR and restriction enzyme digestion. Results: Restenosis rate, defined as ≥50% diameter stenosis, was 29.3%. The overall genotype frequency distributions were in Hardy-Weinberg equilibrium for all variants. Carriers of the 298Asp allele of the eNOS Glu298Asp polymorphism showed a higher frequency of restenosis with an odds ratio of 1.88 (95%CI 1.01-3.51, p=0.043) compared to 298Glu homozygotes. Carriers of the -786C allele of the eNOS -786T>C polymorphism also showed a higher frequency of restenosis with odds ratio of 2.06 (95%CI 1.08-3.94, p=0.028). Other studied genes did not show significant association with coronary in-stent restenosis.

Conclusions: In patients with coronary artery disease, the possession of the 298Asp and -786C variants of the eNOS gene is a risk factor for coronary in-stent restenosis, demonstrating the importance of the nitric oxide system in restenosis.

ORAL CONTRIBUTIONS

805 Drug-Eluting Stents

Monday, March 31, 2003, 9:15 a.m.-10:30 a.m.
Mc Cormick Place, Room S401

805-1 Two-Year Follow-Up of the RAVEL Study: A Randomized Study With the Sirolimus-Eluting Bx VELOCITY Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions

Marie-Claude Morice, Patrick Serruy, Costantino Costantini, Egon Wuefler, William Wijns, Jean Fajadet, Antonio Colombo, Giulio Guagliumi, Ferenc Molnar, Ernesto Ban Hayashi, Sier Juhua M. Seng, Marueth Pein, on behalf of the RAVEL Trial Investigators, Institut Cardiovasculaire Pans Sud, Massy, France.

Background: Sirolimus, a macrolide antibiotic and immunosuppressant, causes late G1 cell cycle arrest. A pilot study using Sirolimus-eluting stents (SES) to treat coronary artery lesions demonstrated almost no neointimal hyperplasia at 12 months. Results from this study were used to design RAVEL, a multicenter, double blind, two-arm, randomized study assessing safety and effectiveness of the Sirolimus-eluting Bx VELOCITY™ stent versus the uncoated Bx VELOCITY™ stent (16 mm).

Methods: The primary endpoint was angiographic late loss at 6 months. The secondary endpoints were major adverse events, lesions demonstrating almost no neointimal hyperplasia at 12 months. Results from this study were used to design RAVEL, a multicenter, double blind, two-arm, randomized study assessing safety and effectiveness of the Sirolimus-eluting Bx VELOCITY™ stent versus the uncoated Bx VELOCITY™ stent (16 mm). Clinical outcomes were assessed at 1 year.

Results: TLR-free - 1 year 95.6
MACE-free - 1 year 93.1
ATLR-free - 1 year 98.3
TVR-free - 1 year 94.1

Conclusion: The QCA data demonstrate virtually no neointimal-in-stent proliferation with event-free survival of 94% at one year in the SES treatment group. Two-year clinical follow-up data will be presented.

805-2 Cost-Effectiveness of Sirolimus Drug-Eluting Stents for the Treatment of Complex Coronary Stenoses: Results From the Randomized SIRIUS Trial

David J. Cohen, Annet Saligne, Chiousu Shi, Louise Glihrta, Ronna B. Beskin, Raoul P. Caputo, Charles O'Shaugnessy, Martin B. Leon, Jeff Moss, Richard E. Kuntz, on behalf of the SIRIUS Investigators, Beth Israel Deaconess Medical Center, Boston, MA, Harvard Clinical Research Center, Boston, MA.

Background: Previous studies have demonstrated that sirolimus drug-eluting stents (DES) dramatically reduce angiographic and clinical restenosis compared with conventional stenting. However, the cost-effectiveness (C/E) of DES in routine clinical practice is unknown. Methods: We prospectively measured medical resource utilization and cost for 1100 PCI patients randomized to either sirolimus DES or bare stents (BS) as part of the SIRIUS trial. Costs were assessed from the U.S. societal perspective, and each DES was assumed to cost $3000/stent. Results: Resource utilization and 1-year cost data for the first 400 randomized patients are displayed below (see Table). Although DES reduced the rate of target vessel revascularization by 62% and follow-up costs by $1500/patient, overall 1-year costs remained higher with DES (p=0.001).

The incremental C/E ratio for DES compared with BS was $5542 per repeat revascularization (RepRev) avoided—similar to the C/E of BS for de novo lesions or brachytherapy for diffuse intrastent restenosis ($5000-$10,000 per RepRev avoided).

Conclusions: 1) In a representative population of PCI patients, sirolimus DES improved clinical outcomes but increased overall healthcare costs by $5542 compared with BS. 2) Nonetheless, considering the quality of life benefits of avoiding restenosis, the C/E of DES compares reasonably with other accepted interventional techniques. 3) Complete 1-year data on the full 1100 pt trial will be available by 303.
Late Incomplete Stent Apposition Following Sirolimus-Eluting Stent: Serial Quantitative Intravascular Ultrasound Analysis From the SIRIUS Trial

Junya Ako, Yasuhito Morino, Yasuhito Honda, Shingo Sonoda, Mitsuuyasu Terashima, Ali Hassan, Martin B. Leon, Jeffrey W. Moses, Steve Osterle, Charles L. Brown, Donald S. Berman, Paul C. Yeck, Peter J. Flaggemer, the CINHUS Investigators, Stanford University, Stanford, CA, Lenox Hill Hospital, New York, NY

Background: Stent incomplete apposition (IA) at follow-up is reported in drug-eluting stents. The aim of this study was to clarify the morphometric IVUS characteristics of late IA.

Methods: IVUS data were obtained from SIRIUS, a prospective, randomized, multicenter trial. IA was defined as >1 stents separated from vessel wall with evidence of blood specks behind the stents. The maximal stent/stent gap, maximal axial length, and arc degrees of incompletely apposed stunts were quantified. IA index was defined as total lumen area divided by lumen area within the stent. Persistent IA was defined in late follow-up when IA was observed at both baseline and 8-month follow-up. Late IA was defined as new IA detected only at follow-up.

Results: Of 130 serial cases, there were 19 follow-up IA segments in 17 patients (BMS 6, SES 11) available for quantitative analysis. While persistent IA was observed in both groups (BMS 8, SES 4), late IA was only seen in SES. In-lesion stent area was significantly larger in late IA than persistent IA (P<0.05), and 2 late IA showed pathologic positive remodeling (20% increase in vessel area compared to baseline). All persistent IAs were located at stent edges, whereas 77% of late IAs occurred at single or multiple mid-stent segments (P<0.01).

Conclusions: Differences in vessel wall biology of this phenomenon compared to persistent IA were observed.

<table>
<thead>
<tr>
<th>Persistent IA (n=8)</th>
<th>Late IA (n=4)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gap, mm²</td>
<td>0.9±0.17</td>
<td>0.4±0.12</td>
</tr>
<tr>
<td>Arc, °</td>
<td>107±22.5</td>
<td>97±14.0</td>
</tr>
<tr>
<td>Length, mm</td>
<td>1.9±0.65</td>
<td>2.8±1.7</td>
</tr>
<tr>
<td>Follow-up lumen area, mm²</td>
<td>8.3±2.65</td>
<td>9.8±1.4</td>
</tr>
<tr>
<td>Follow-up vessel area, mm²</td>
<td>19.0±7.3</td>
<td>17.0±2.5</td>
</tr>
<tr>
<td>Vessel area, mm²</td>
<td>-0.007±0.01</td>
<td>0.34±0.88</td>
</tr>
<tr>
<td>IA index</td>
<td>1.1±0.07</td>
<td>1.1±0.02</td>
</tr>
</tbody>
</table>

10:15 a.m.

An Overlapping Multiple Sirolimus-Eluting Stents: Impact Angiographic and Clinical Outcomes? Insights From the SIRIUS Trial

Ujilla Weiss, Jeffrey W. Moses, Jeffrey J. Popma, Ureg Hanauer, Robert L. Wiener, Barry Cohen, Hooman Madjoudj, David Roberts, Martin B. Leon, Lenox Hill Hospital Heart and Vascular Institute of New York and Cardiovascular Research Foundation, New York, NY

Background: Although previous clinical studies have demonstrated a dramatic reduction in subsequent restenosis (Res) after sirolimus-eluting stent (SES) implantation, little is known about the impact of overlapping multiple stents on angiographic and clinical outcomes.

Methods: In the randomized, double-blind SIRIUS trial, in longer lesions or to stent failure, the use of overlapping SES was permitted. The aim of this study was to compare angiographic and clinical outcomes in patients receiving overlapping SES vs. single SES.

Results: At 12 months, overlapping SES was associated with a lower rate of Res (8.8% vs 42.7%), target lesion revascularization (4.7% vs 8.3%), and MACE (8.6% vs 23.1%). The rate of Res in the overlapping SES group was significantly lower (P<0.001) as compared to single SES controls.

Conclusions: In the SIRIUS trial, overlapping SES was associated with a lower rate of Res, indicating a potential benefit for this strategy in the management of complex lesions.

OCTAL CONTRIBUTIONS

808 Restenosis: Basic Mechanisms
Monday, March 31, 2003, 9:15 a.m.-10:30 a.m.
McCormick Place, Room S403

808-1 Mobilized Bone Marrow Stem Cells Accelerate Reendothelialization, Reduce Vascular Inflammation, and Prevent Restenosis After Intravascular Radiation
Hyun-Jae Cho, Hyo-Soo Kim, Dae-Hee Kim, Seil Oh, In-Ho Chae, Byung-Hee Oh, Myoung-Mook Lee, Young-Bea Park, Yun-Shik Choi, Seoul National University College of Medicine, Seoul, South Korea, Clinical Research Institute, Seoul National University Hospital, Seoul, South Korea

Background: Stem cell therapy may provide new possibilities for the treatment of vascular disorders. We investigated a role of mobilized stem cells in the healing process after intravascular irradiation, the condition of few replicating endothelial cells in adjacent area.

Methods: 1% cholesterol-diet fed male New Zealand White rabbits with injured iliac artery were divided into two groups. The GM-CSF group (n=15) received GM-CSF (62g/d) daily for 1 week, beginning 7 days before injury. Control group (n=18) received human albumin. One iliac artery was subjected to intravascular radiation via 810nm laser and the contralateral iliac artery to balloon angioplasty control. Morphometry and immunohistochemistry were done. Peritumoral mononuclear cells (MNCs) were isolated from blood just before vessel harvest, analyzed FACS and cultured for 4 weeks.

Results: In control group, intravascular therapy reduced neointimal hyperplasia (0.09±0.05 vs 0.26±0.11 mm², P<0.01) but delayed reendothelialization and promoted inflammatory cell infiltration. After GM-CSF pretreatment, reendothelialization index (defined as CD31 stained endothelial perimeter) recovered to 81±13% (n=7), whereas 30±11% in the control group (n=9) (P<0.01) and RAM1-positive cell (macrophage) infiltration reduced in media at 14 days. (12±7 vs 29±10%, P<0.01) Also, significant reduction in neointimal thickening was observed. (0.04±0.01 vs 0.09±0.03 mm², P<0.01) FACS analysis showed that 24% of MNCs were positive for CD45 and 13% positive for CD43 in the GM-CSF group but all negative in the control group. Cytokine levels were assessed with cytokine array, and GM-CSF up-regulated the IL-10 from peripheral blood mononuclear cells (PBMCs) in comparison with non-stimulated cells (P<0.01).

Conclusions: GM-CSF pretreatment mobilizes stem cells, accelerates reendothelialization and reduces inflammatory cell infiltration after intravascular radiation therapy, which suggests that stem cell therapy is a promising strategy for enhancing vascular healing process after angioplasty.

9:30 a.m.

808-2 Activation of Peroxisome Proliferator-Activated Receptor and Gamma Inhibits Neointimal Formation in a Diabetic Rat Carotid Artery Injury Model
Kai Wang, Liming Fan, Thammy Thang, Gary D. Roudet, Xiaorong Zhou, A. Michael Lincoff, Eric J. Topol, Marc S. Penn, The Cleveland Clinic Foundation, Cleveland, OH

Background: Peroxisome Proliferator-Activated Receptor γ (PPARγ) is member of the nuclear receptor superfamily of ligand-dependent transcription factors. Thiazolidinediones, which are anti-diabetic agents and high-affinity ligands for PPARγ, have been shown to inhibit the growth of vascular smooth muscle cells. In this study, the role of PPARγ on neointimal formation was studied in a diabetic rat carotid artery injury model.

Methods and Results: Balloon injury of carotid artery was performed in the Zucker fat rats (diabetic) and lean rats (non-diabetic) using the standard method. In treatment groups, rosiglitazone (20mg/kg/day), PPARγ agonist, was given orally 1 week before injury through the 21 days follow-up. The animals were sacrificed after 21 days, and morphometric analysis was performed. Lipids and glucose assay was performed at baseline and 21 days. Neointimal formation was significantly decreased by the administration of rosiglitazone, but only in the diabetic rat cohort (Table). There was no difference of body and glucose levels between baseline and 21 days in the diabetic rats.

Conclusion: The activation of PPARγ inhibits neointimal hyperplasia in a diabetic rat carotid artery injury model.