A Phase I Open-Label Dose Escalation Trial of a Monoclonal Antibody Against Tissue Factor (Sunol CH36) in Stable Coronary Artery Disease: Results of the PROXIMATE-TIMI 27 Trial

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Tissue factor (TF) is a critical participant in the genesis of acute coronary syndromes. Sunol CH36 is a chimeric monoclonal antibody to TF that blocks binding of factor X to TF-VIIa. This novel anticoagulant had not yet been tested in humans. METHODS: We assessed the safety & pharmacokinetics of CH36 in pts with stable CAD receiving aspirin. The safety analysis included all adverse events (AEs) with a focus on bleeding during 7 weeks post-dose. RESULTS: Five doses of CH36 were given IV x 1 among 26 subjects (3-8 per dose tier). Preliminary results show no major bleeding (>2 g/dl, stall in Hgb). Spontaneous minor bleeding exhibited a dose-related pattern (Table). Notably, most bleeding events were clinically consistent with platelet-mediated bleeding (eg. gum/ tongue). Through expected interaction with a human tissue-factor based assay, CH36 exhibited a dose-related prolongation of the prothrombin time. There were no other lab abnormalities or re-related AEs. Human anti-chimeric antibody was not elevated at 7 wks. PK data will also be presented with the final study results. CONCLUSION: In this initial experience in humans, CH36 exhibited dose-related anticoagulant effects manifest with a short half-life at doses <0.1 mg/kg. We postulate that the platelet-mediated bleeding observed with this potent inhibitor of thrombin generation reflects important networking between thrombin & platelet pathways that may prove clinically relevant with this novel class of anticoagulants.

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<th>Dose Sunol CH36 (mg/kg)</th>
<th>Enrolled (N)</th>
<th>Major Bleeding (subjects)</th>
<th>Spont. Minor Bleeding (subjects)</th>
<th>Gum/tongue bleeding</th>
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Medullar Neurostimulation Is a Safe Alternative for Refractory Angina

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Refractory angina defined as severe angina, resistant to maximum medical therapy and unsuitable for further revascularization. Medullar neurostimulation (MSN), with proved beneficial effects in a series of chronic painful conditions, could theoretically become a safe and effective therapeutic alternative. To assess whether patients with refractory angina (RA), improve their quality of life without increasing morbidity-mortality, 34 patients meeting criteria for RA were studied after a minor surgical procedure to implant a medullar neurostimulator. Consistent with inclusion criteria, all patients had persistent ischemia, 56% were males, with a mean age of 70 ± 6 y; 97% had hypertension; 81% dyslipidemia, 78% diabetes, 70% peripheral arteriopathy and 42% chronic renal failure. CHD had lasted 9 ± 5 years on average, 94% had three vessels disease and 72% had been previously revascularized. Objective and subjective clinical and functional variables, including a quality of life scale (Euroquol test) were assessed at baseline (B) and after 36 months of follow-up (F). Following neurostimulation both functional classes improved NYHA (3.2 ± 0.8 B vs. 1.9 ± 0.8 F; p=0.001) and Canadian (3.5 ± 0.5 to B 1.7 ± 0.8 F; p<0.001), angina dropped from 10 to 7 episodes/week (p<0.001), ejection fraction raised from 36.7 ± 8.9 to 43.7 ± 2.5 (p<0.03), and exercise time increased from 2.2 ± 1.6 to 4.2 ± 1.8 minutes (p<0.01). Health benefit on mobility (2.19 ± 0.3 B to 1.44 ± 0.5 F), personal care (2.03 ± 0.6 B vs. 1.11 ± 0.4 F), daily activity (3.3 ± 0.5 B vs. 1.4 ± 0.4 F), chest pain (2.9 ± 0.2 vs. 1.3 ± 0.4 F) and depression/anxiety parameters (2.7 ± 0.5 B vs 1.6 ± 0.5 F), improved by 81% (p=0.001). No differences were found in body mass index or isotopic perfusion studies when available for comparison (6 patients). Up to 88% has survived 36 months, and for the time being only 5 p have been hospitalized for cardiac causes (15.6%; p<0.005).

In conclusion, our study shows that in refractory angina, medullar neurostimulation grants mid-term improvement in quality of life, clinical, and functional parameters. Medullar neurostimulation is an alternative therapy with a small impact on mortality and morbidity in selected high risk symptomatic patients.

861-4

ORAL CONTRIBUTIONS

New Observations in Acute Myocardial Infarction Trials

Wednesday, March 10, 2004, 8:30 a.m.-10:00 a.m.
Morial Convention Center, Room 355

869

Relationship Between Time to Reperfusion, ST-Segment Resolution, Myocardial Blush Scores and Mortality With Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction: Results From the CADILLAC Trial

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Background: Achieving optimum microvascular reperfusion is important for optimizing outcomes with primary PCI. The relationship between time to reperfusion and measures of microvascular reperfusion with primary PCI has not been studied.

Methods: The CADILLAC Trial randomized 2,082 pts with AMI to PTCA vs stenting +/- abciximab. Analyses of myocardial blush (MB) from post-PCI cineangiograms (n=1,256) and ST-segment resolution (STR) from pre and post-PCI ECGs (n=700) were performed at core laboratories.

Results: Early time to reperfusion (<3 vs 3-6 vs >6 hrs) was associated with a higher frequency of Grade 2-3 MB (56% vs 53% vs 44%, p=0.033) and a higher frequency of complete (70%) STR (64% vs 68% vs 47%, p=0.0002). Complete STR (>70% MB) was associated with a higher frequency of Grade 2-3 MB (56% vs 40%, p=0.0007), although 40% of pts with poor STR had good blush scores and 44% of pts with complete STR had poor blush scores. One year mortality was lowest with optimum microvascular reperfusion (complete STR and Grade 2-3 MB) and highest with poor microvascular reperfusion (poor STR and Grade 0-1 MB) (0.6% vs 9.9%, p=0.006). Mortality was excellent with optimal microvascular reperfusion regardless of time to reperfusion (<3 vs ≥3 hrs) (0% vs 1.0%, p=NS), but time to reperfusion did impact mortality in patients with poor microvascular reperfusion (5.9% vs 11.9%, p=0.54).

Conclusion: Early time to reperfusion is associated with a greater likelihood of successful microvascular reperfusion after primary PCI. Delayed time to reperfusion negatively impacts mortality, only in patients in whom successful microvascular reperfusion cannot be restored. While STR and MB are highly correlated, the significant number of pts with discordant data suggest that these 2 methods measure different aspects of microvascular reperfusion. Optimum survival benefit requires achievement of both complete STR and Grade 2-3 MB.

867

Impact of Intravenous Beta-Blockade During Primary Percutaneous Intervention on Convalescent Left Ventricular Function


Background: We have shown that intravenous (IV) beta-blockers (BB) administration during primary percutaneous intervention (PCI) imparts a survival benefit, an effect limited to patients not on chronic oral β-blockade. Whether periprocedural IV BB also improve myocardial recovery is unknown. Methods and Results: In the CADILLAC trial, 2,082 patients with AMI were randomized to either stenting or angioplasty, +/−abciximab. IV BB were used in 1,136 patients (54.5%, BB+), and not in the remaining 946 patients (45.5%, BB−). Paired left ventriculograms were available at baseline and at 7-month follow-up in 230 and 233 BB+ and BB− patients, respectively.

Baseline LVEF was lower in BB+ patients, though follow-up LVEF was similar in both groups corresponding to a significantly greater incremental improvement in LVEF in the BB+ group (Figure). The increase in LVEF from baseline to follow-up in BB+ group was most pronounced in patients not taking oral BB prior to admission. In patients maintained on BB prior to admission, the change in LVEF was similar in BB+ and BB− patients. By multivariate analysis, IV BB in patients not receiving oral BB prior to admission was an independent predictor of greater increase in LVEF from baseline to 7-month follow-up (β coefficient=3.24, p<0.0001).

Conclusions: In patients undergoing catheter-based reperfusion for myocardial infarction,