Beneficial Effects of Complement Inhibition With Soluble Complement Receptor 1 (TP10) During Cardiac Surgery

Is There a Gender Difference?

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Background—TP10, a potent inhibitor of complement activation during cardiopulmonary bypass (CPB) has been shown to significantly reduce the incidence of death and myocardial infarction (MI) in high-risk male patients undergoing cardiac surgery. However, the effect of TP10 in females was undefined because of the limited number of females studied. To examine the possibility of a gender effect, this phase 2 multi-center trial was undertaken to determine whether TP10 would also limit ischemic damage in a larger sample size of high-risk females undergoing cardiac surgery on cardiopulmonary bypass (CPB).

Methods and Results—This prospective, double-blind, placebo-controlled, multi-center trial involved 297 high-risk (urgent surgery, CABG + Valve, reoperations, ejection fraction <30%) female patients randomized to receive a 5 mg/kg dose of TP10 (n=150) or placebo (n=147) as a 30-minute intravenous infusion before surgery. The primary end point was the incidence of death or MI at 28 days after surgery. Complement activation was assessed by levels of CH50 and SC5b-9 during and after CPB. TP10 was well tolerated and there were no differences in the safety profiles of the 2 groups. Although TP10 effectively suppressed complement activation (at 2 hours after CPB CH50 (mean±SD % change from baseline) 50±17% placebo versus 4±14% TP10; P=0.0001; SC5b-9 (ng/mL) 917±1067 placebo versus 204±79 TP10; P=0.0001), there was no difference in the primary end point between the groups (17% placebo versus 21% TP10; P=0.2550).

Conclusions—The benefits of TP10 appear to be gender-related. and mechanisms other than complement activation may be responsible for myocardial injury in high-risk female patients during cardiac surgery on CPB. (Circulation. 2007; 116[suppl I]:I-83–I-88.)

Key Words: ischemia □ inflammation □ extracorporeal circulation

Activation of complement during cardiopulmonary bypass (CPB) initiates a systemic inflammatory response, which contributes to postoperative morbidity and mortality.1 TP10, a soluble derivative of human complement receptor type 1, is a potent inhibitor of both the classical and alternative complement pathways.2 It has been shown to effectively inhibit complement activation in previous studies in patients undergoing cardiac surgery on CPB.3 TP10 exerts its biological actions by accelerating the decay of the convertases that activate C3 and C5, thus inhibiting the production of C5b-9, which is deposited in areas of infarcted and ischemic myocardium and contributes to cell lysis and death.2

In a previous prospective, randomized, multi-center, phase 2 trial involving 564 high-risk adult patients undergoing cardiac surgery, in male patients, TP10: (1) reduced the incidence of death or myocardial infarction (MI) by 36% in all types of cardiac surgery; (2) reduced the incidence of death or MI during coronary artery bypass graft (CABG) surgery by 43%; and (3) eliminated the need for prolonged IABP support during CABG + Valve surgery.3 However, the favorable effects of TP10 were not seen in the limited number of female patients in this trial.

Female gender has been found in previous studies to be an independent risk factor for mortality after CABG and CABG + Valve surgery.4–7 Although outcomes in women undergoing CABG surgery have improved over the past decade, women still have a higher incidence of mortality, perioperative Q wave MIs, increased inotropic usage, prolonged...
ventilatory support, and longer hospital and intensive care unit (ICU) stays. One possible reason for the apparent lack of improvement in females in the initial TP10 trial was that only 28% of the patients studied were female. Hence, it is unclear as to whether the lack of benefit from TP10 in women was attributable to a gender effect or to a limited sample size. Accordingly, a females-only phase 2 clinical trial involving high-risk females undergoing cardiac surgery on CPB was undertaken to determine whether the favorable effects of TP10 could also be seen in a larger cohort of women by: (1) inhibiting complement activation; and (2) reducing mortality and the incidence of MIs.

Methods

Study Design

This was a prospective, multicenter, randomized, double blind, placebo-controlled, phase 2 trial in adult females undergoing high risk cardiac surgery on CPB in the United States. Enrollment continued from May 2004 to October 2005. Approval was obtained from the Institutional Review Boards of all the centers and written informed consent was obtained from each study subject. Inclusion criteria included female patients undergoing cardiac surgery on CPB requiring redo sternotomy, urgent or emergent CABG in the absence of an evolving MI, left main stenosis >50%, 3-vessel coronary disease with NYHA Class III or IV angina, or the combination of CABG + Valve repair or replacement. Exclusion criteria included the presence of an MI within 72 hours before randomization, the presence of a left bundle-branch block (LBBB), the need for isolated hospital and ICU length of stay, and changes in ECG.

Myocardial Infarction and Biological Assays

A diagnosis of an MI was based on CK-MB enzyme levels over time with serial ECGs used to classify an MI into Q and non-Q MIs. All ECG and CK-MB data were forwarded to a core laboratory (St. Louis University, St. Louis, Mo) for adjudication and final blinded interpretation of an MI. The definition of a perioperative MI was made within the initial 72 hours after surgery if CK-MB >10 times the upper limit of normal (ULN). A diagnosis of a Q wave MI was based on the Minnesota Code Classification using an adaptation of the Nova code for serial comparison. A 2-grade worsening of the code qualified as a Q wave MI. Persistent new LBBB in the 72 hours after surgery was classified as a Q wave MI. The diagnosis of an MI after 72 hours after surgery required elevation of CK-MB >2 times the ULN and new ECG findings or chest pain or an anginal equivalent.

Serum and plasma samples for biological assays were centrifuged and stored at −80°C until assayed. Hemolytic assays (CH50) were performed at a central laboratory as previously described. Plasma levels of SC5b-9 were also analyzed at a central laboratory using a specific biotinylated monoclonal antibody enzyme-linked immunoabsorbent assay.

Schedule of Study Parameters

Complete blood counts, biochemistry profiles, and urinalyses were obtained before surgery, 24 hours after the end of the drug infusion, and 24 hours before discharge from the hospital. CK-MB was obtained every 8 hours for the first 24 hours after surgery. A 12-lead ECG was recorded before and each day after surgery until postoperative day 5 and again on postoperative day 28. All adverse events were recorded for 28 days after surgery.

Statistical Analyses

Data were summarized using mean±SD for continuous variables and the number and percentage for categorical variables using Statistical Analysis Systems (SAS, version 8.2 or higher). Statistical significance was defined as P<0.05. All efficacy analyses were performed on intent to treat (ITT) population, whereas safety analyses were done on the safety population (as treated). The primary efficacy variable, the composite incidence of death or MI, was analyzed using a 1-sided Fisher exact test to compare the placebo and TP10 groups intent to treat (ITT). In addition, 95% confidence intervals for individual rates and differences in rates (placebo minus 5 mg/kg TP10) were calculated. Subgroup analyses based on the type of surgery, race, age, and CK-MB levels were performed using a Cochran-Mantel-Haenszel test. Secondary efficacy variables were analyzed with Cox proportional hazard models for time to event variables. Time to death or MI was analyzed using analysis of variance (ANOVA). SC5b-9 and CH50 were summarized and a percent change from baseline was calculated. A comparison of TP10 to placebo was analyzed using an ANOVA or Wilcoxon rank sum test as appropriate. Adverse events were coded using the Medical Dictionary for Regulatory Affairs (MedDRA; Version 5.1) and summarized by organ class and treatment group. The study was powered assuming a reduction in the primary end point event rate from 25% in the placebo group to 14% in the TP10 group using a Fisher exact test, the test was 1-tailed at the 0.05 level with approximately 75% power. Because the study was exploratory, the power was less than the minimum of 80% normally used for confirmatory studies.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

### TABLE 1. Patient Disposition

<table>
<thead>
<tr>
<th></th>
<th>Placebo, n (%)</th>
<th>TP10, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient screened</td>
<td>153 (100)</td>
<td>156 (100)</td>
<td>309 (100)</td>
</tr>
<tr>
<td>Safety population</td>
<td>144 (100)</td>
<td>153 (100)</td>
<td>297 (100)</td>
</tr>
<tr>
<td>ITT population</td>
<td>147</td>
<td>150</td>
<td>297</td>
</tr>
<tr>
<td>PP population</td>
<td>140</td>
<td>146</td>
<td>286</td>
</tr>
<tr>
<td>Completed protocol</td>
<td>133 (92)</td>
<td>147 (96)</td>
<td>280 (94)</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>11 (8)</td>
<td>6 (4)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>Consent withdrawal</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>6 (4)</td>
<td>3 (2)</td>
<td>9 (3)</td>
</tr>
</tbody>
</table>

ITT indicates intent-to-treat; PP, per-protocol.
Aprotinin and Amicar.

ACE-inhibitor was used in 60% and nearly a third received antiplatelet therapy, use was comparable between the groups (Table 3). All patients received some form of antiplatelet therapy, and the incidence of diabetes mellitus, ejection fraction, or the duration of CPB and cross clamp times. Concomitant medication involving cardiovascular disease. This may be one explanation why women have failed to show clinical benefits with complement activation in high-risk female patients undergoing cardiac surgery other than complement activation are responsible for myocardial injury in female patients undergoing cardiac surgery on CPB; and (3) limitations in the study design minimized the potential benefits of complement suppression.

Women have historically been under-represented in trials involving cardiovascular disease. This may be one explanation why women have failed to show clinical benefits with ACE inhibitors and β-blockers in trials where these drugs were shown to have improved outcomes in males. How-

TABLE 3. Adjuvant Pharmacological Therapy

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=147)</th>
<th>TP10 (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet (%)</td>
<td>147 (100)</td>
<td>150 (100)</td>
</tr>
<tr>
<td>B-Blocker (%)</td>
<td>147 (100)</td>
<td>150 (100)</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>147 (100)</td>
<td>150 (100)</td>
</tr>
<tr>
<td>Heparin (%)</td>
<td>132 (90)</td>
<td>145 (97)</td>
</tr>
<tr>
<td>Perioperative insulin infusion (%)</td>
<td>120 (83)</td>
<td>125 (82)</td>
</tr>
<tr>
<td>ACE-inhibitor (%)</td>
<td>88 (60)</td>
<td>100 (67)</td>
</tr>
<tr>
<td>Aprotinin (%)</td>
<td>46 (31)</td>
<td>48 (32)</td>
</tr>
<tr>
<td>Amicar (%)</td>
<td>55 (37)</td>
<td>58 (39)</td>
</tr>
</tbody>
</table>

Population: Intent-to-treat values are mean ± SD.

CABG indicates coronary artery bypass graft; CPB, cardiopulmonary bypass.

Results

Patient disposition is summarized in Table 1. Of 297 treated subjects, 17 discontinued the study for consent withdrawal,^3^ death,^4^ or being lost to follow up.^

The patient profiles are reviewed in Table 2. The groups did not differ in age, the type or urgency of surgery, the incidence of diabetes mellitus, ejection fraction, or the duration of CPB and cross clamp times. Concomitant medication use was comparable between the groups (Table 3). All patients received some form of antiplatelet therapy, β-blockers, and statins. Over 80% received intravenous insulin infusions to maintain tight glycemic control. An ACE-inhibitor was used in 60% and nearly a third received Aprotinin and Amicar.

The effects of TP10 on complement activity are shown in Figures 1 and 2. Figure 1 shows the CH50 at various times as a percentage of the baseline preinfusion values which were 317±96 (mean±SD; n=37) for placebo and 284±95 (n=50) for TP10 subjects. CH50 measures the capacity of the complement in serum from a patient to lyse complement-fixed erythrocyte target cells in vitro. The decrease in CH50 seen in the placebo group reflects systemic complement activation during CPB and the resulting depletion of approximately 50% of the baseline complement activity which is subsequently replenished over a period of a few days. Treatment with TP10 resulted in a marked suppression of CH50 as compared with the placebo group starting at 5 to 10 minutes after the initiation of CPB and continuing for 3 days after surgery. In TP10 patients, measured CH50 was 1.8% of baseline at 5 to 10 minutes on CPB (P<0.0001 versus placebo), 10.1% of baseline at 24 hours after surgery (P<0.0001 versus placebo), and 64.6% of baseline at 3 days after surgery (P<0.0001 versus placebo).

Figure 2 shows the change from baseline of plasma SC5b-9 concentrations, a measure of systemic complement activation ongoing in patients. Baseline preinfusion SC5b-9 concentrations were 493±1060 ng/mL (mean±SD; n =39) in the placebo group and 400±745 ng/mL (n=47) in the TP10 group. Complement activation was greatest at 5 to 10 minutes after CPB, as evidenced by increased SC5b-9 levels in the placebo patients, and was profoundly inhibited at this same time in patients receiving TP10 (P<0.0001). By 24 hours after infusion, SC5b-9 levels had returned to near or below baseline levels in the placebo group. Based on SC5b-9 plasma concentrations, there was no evidence of systemic complement activation in the TP10-treated group at any time point assessed in the study. Although TP10 significantly inhibited complement activation, it had no effect on clinical outcomes (Table 4). There was no difference in the primary end point of death or MI (17% placebo versus 21% TP10; P=0.255). TP10 patients had fewer deaths (1% versus 3%; P=0.210) but a higher incidence of MIs (16% placebo versus 21% TP10; P=0.293). There was no difference in the incidence of atrial fibrillation or ICU or hospital LOS. Analysis of the primary efficacy end point in subgroups based on type of surgery (CABG only versus CABG + Valve) did not reveal significant advantage to TP10 over placebo in this patient population. In CABG only patients, the incidence of death or MI was 17.2% and 21.8% in the placebo and TP10 treated group, respectively. Similarly, in patients who underwent CABG + Valve surgery, the incidence of death or MI was 16.2% in the placebo versus 17.5% in TP10.

TP10 was well tolerated with a similar safety profile in TP10 and placebo-treated groups. The number of patients with at least one serious adverse event was similar in both groups (43% placebo versus 32% TP10). The incidence of adverse events, including infection rate, were also similar for all organ systems in both groups (Table 5).

Discussion

In this phase 2 trial, TP10 effectively suppressed complement activation in high-risk female patients undergoing cardiac surgery on CPB. TP10 was safe and resulted in no increase in adverse events. However, in this cohort of female patients, TP10 had no effect on the primary combined end point of death and MI. Possible explanations for these findings are (1) that the benefits of TP10 are gender-related; (2) mechanisms other than complement activation are responsible for myocardial injury in female patients undergoing cardiac surgery on CPB; and (3) limitations in the study design minimized the potential benefits of complement suppression.
ever, when data were pooled from 3 separate studies involving β-blockers resulting in a larger sample size, similar survival benefits were seen in men and women.13 Hence, larger sample sizes may be necessary to show beneficial effects in women with cardiovascular diseases. Is it possible that the sample size in this trial resulted in insufficient statistical power to show improved outcomes with TP10? In determining the sample size for this trial, it was hypothesized that the event rate of death or MI in the placebo group would be at least 25% based on outcome data in the previous TP10 trial.3 However, in this trial, the primary event rate was only 17%. Why then did the placebo group have such few events? One possible explanation is that the participants in this trial had more optimal medical management in the perioperative period. One hundred percent of patients in both treatment arms received antplatelet therapy, β-blockers, and statins in the perioperative period. Over 80% of patients in either group received intravenous insulin infusions to maintain tight glycemic control during the surgery and in the ICU, and ACE inhibitors were used in 60% of patients. It is well known that these agents can independently reduce perioperative morbidity and mortality after cardiac surgery and may have been responsible for the low event rate in the placebo group.14–18

Patients in this study were excluded from participation if they had an MI within 72 hours before surgery to better determine the incidence of postoperative MIs based on CK-MB levels. However, by doing so, we may have eliminated those patients with active ischemia that may have benefited most from complement suppression. Furthermore, CK-MB may not be the most sensitive marker of perioperative ischemia in female patients. Wiviott and coworkers have shown that in patients with myocardial necrosis, men were more likely to have elevated CK-MB and troponin levels, whereas women were more likely to have elevated C-reactive protein (CRP) and brain natriuretic peptide (BNP) levels, reflecting a higher incidence of small vessel disease, vascular inflammation, and congestive heart failure.19 Is there a difference in the response to complement activation between males and females? Two studies suggest that gender may play a role in the effects of complement activation. Rugonfalu-Kiss and coworkers looked at the effects of mannose-binding lectin (MBL) on restenosis rates in males and females after carotid endarterectomies (CEA).20 MBL activates the lectin pathway of complement, which ultimately stimulates the classical complement pathway before the C3 activation step. In this study, 123 patients undergoing CEA were followed by serial carotid duplex sonography. Patients homozygous for the normal MBL AA genotype had a higher risk for early carotid restenosis. Female carriers with the AA genotype had a significantly higher incidence of restenosis than males.
TABLE 4. Clinical Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>TP10</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or MI (%)</td>
<td>25 (17)</td>
<td>31 (21)</td>
<td>0.255</td>
</tr>
<tr>
<td>Death (%)</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>0.210</td>
</tr>
<tr>
<td>MI (%)</td>
<td>23 (16)</td>
<td>31 (21)</td>
<td>0.293</td>
</tr>
<tr>
<td>Intensive care unit LOS (days)</td>
<td>3.09 ± 3.04</td>
<td>3.42 ± 3.72</td>
<td>0.405</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>8.66 ± 7.00</td>
<td>9.58 ± 8.83</td>
<td>0.346</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>45 (31)</td>
<td>48 (31)</td>
<td>0.352</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Another example of the effect of gender on complement activation was provided by Lennon and coworkers in the rabbit aorta.21 In rabbit thoracic aortic rings preconstricted with phenylephrine, infusion of human serum resulted in complement-mediated loss of endothelium-dependent relaxation. The loss of endothelial-dependent relaxation was greater in males than females. This study strongly suggests that males are more susceptible than females to the acute effects of complement activation on endothelial function. The mechanism for these actions is still unknown.

In addition to differences in response to complement activation by gender, the mechanism by which complement is activated may also be important in determining clinical outcomes after cardiac surgery. Despite significantly more activation of SC5b-9 on CPB, there was no difference in the primary outcomes between the placebo and TP10 female patients. This suggests that there may be a difference in the effects of generalized complement activation that is seen by merely being on CPB and localized complement activation that is seen in myocardial tissue due to ischemia. The mechanism for the ability of TP10 to limit myocardial necrosis most likely results from its ability to limit the inflammatory response in ischemic myocardial tissue. Weissman and coworkers have demonstrated in a rat model that pretreatment with TP10 before ischemia significantly decreased leukocytes in the periinfarct zone and completely abolished membrane attack complexes deposited in ischemic and infarcted tissue.23 TP10 also acts to directly inhibit the deposition of C5b-9 in the endothelium of ischemic myocardium on repertusion, thus improving endothelial function and decreasing the potential for cell death.23 C5 complement inhibition has been shown to prevent apoptosis in experimental models of acute ischemia.24 It is conceivable that complement inhibition during cardiac surgery may improve long-term outcomes by altering mechanisms of apoptosis. In support of this theory is the data from the Phase 2 Comma Trial in which pexelizumab, a C5 inhibitor, did not reduce infarct size in patients undergoing primary percutaneous coronary interventions for an MI after 72 hours, but significantly reduced 90 day mortality.25 In our trial, the follow-up period was only 28 days. It is conceivable that there may have been a difference in long-term survival, had the follow-up period been extended.

What can we learn from this trial regarding complement activation in females during cardiac surgery on CPB? TP10 effectively suppresses complement activation in female patients undergoing cardiac surgery on CPB. Despite effective complement inhibition in the TP10 group, there was no difference in clinical outcomes relative to placebo. This suggests that generalized complement activation induced by merely being on cardiopulmonary bypass may not contribute to myocardial infarction in these patients. This study also supports the results of other trials, which have demonstrated that outcomes for female patients after CABG surgery are improving and may be enhanced by optimizing perioperative medical therapy. What will be the role of complement suppression therapy be in these patients? Recent phase 2 clinical trials using the C5 inhibitor pexelizumab in CABG patients showed no improvement in the composite primary end point of death, MI, LV dysfunction, or CNS events at 30 days.26,27 However, post-hoc analysis of these trials revealed that pexelizumab did reduce the incidence of death or MI in patients with 3 or more risk factors and in those with prolonged cross clamp times.28,29 These studies, as well as the data from our previous TP10 trial in males suggest that patients with the highest risk, including those with prolonged CPB and cross clamp times, patients with ongoing or recent (>48 hours) ischemia, and those with reduced left ventricular function, will benefit most from anticomplement therapy. Therefore, future trials with TP10 should target these high-risk patients of both genders as we strive to define those patients that will benefit most from this therapy.

TABLE 5. Incidence Of Adverse Events By MedDRA System Organ Class

<table>
<thead>
<tr>
<th>Organ Class</th>
<th>Placebo</th>
<th>TP10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event (%)</td>
<td>144 (100)</td>
<td>152 (99)</td>
</tr>
<tr>
<td>Cardiac (%)</td>
<td>123 (85)</td>
<td>126 (82)</td>
</tr>
<tr>
<td>Respiratory (%)</td>
<td>111 (77)</td>
<td>115 (75)</td>
</tr>
<tr>
<td>Gastrointestinal (%)</td>
<td>108 (75)</td>
<td>117 (76)</td>
</tr>
<tr>
<td>Vascular (%)</td>
<td>75 (52)</td>
<td>91 (59)</td>
</tr>
<tr>
<td>Blood and lymphatic (%)</td>
<td>74 (51)</td>
<td>65 (42)</td>
</tr>
<tr>
<td>Nervous system (%)</td>
<td>49 (34)</td>
<td>58 (38)</td>
</tr>
<tr>
<td>Psychiatric (%)</td>
<td>30 (21)</td>
<td>32 (21)</td>
</tr>
<tr>
<td>Endocrine (%)</td>
<td>7 (5)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Infection</td>
<td>8 (6)</td>
<td>6 (4)</td>
</tr>
</tbody>
</table>

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Disclosures

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References

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