Clinical Investigation and Reports

The VIVA Trial

Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis

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Background—Recombinant human vascular endothelial growth factor protein (rhVEGF) stimulates angiogenesis in animal models and was well tolerated in Phase I clinical trials. VIVA (Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis) is a double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of intracoronary and intravenous infusions of rhVEGF.

Methods and Results—A total of 178 patients with stable exertional angina, unsuitable for standard revascularization, were randomized to receive placebo, low-dose rhVEGF (17 ng·kg\(^{-1}\)·min\(^{-1}\)), or high-dose rhVEGF (50 ng·kg\(^{-1}\)·min\(^{-1}\)) by intracoronary infusion on day 0, followed by intravenous infusions on days 3, 6, and 9. Exercise treadmill tests, angina class, and quality of life assessments were performed at baseline, day 60, and day 120. Myocardial perfusion imaging was performed at baseline and day 60. At day 60, the change in exercise treadmill test (ETT) time from baseline was not different between groups (placebo, +48 seconds; low dose, +30 seconds; high dose, +30 seconds). Angina class and quality of life were significantly improved within each group, with no difference between groups. By day 120, placebo-treated patients demonstrated reduced benefit in all three measures, with no significant difference compared with low-dose rhVEGF. In contrast, high-dose rhVEGF resulted in significant improvement in angina class (P<0.05) and nonsignificant trends in ETT time (P=0.15) and angina frequency (P=0.09) as compared with placebo.

Conclusions—rhVEGF seems to be safe and well tolerated. rhVEGF offered no improvement beyond placebo in all measurements by day 60. By day 120, high-dose rhVEGF resulted in significant improvement in angina and favorable trends in ETT time and angina frequency. (Circulation. 2003;107:1359-1365.)

Key Words: angiogenesis ▪ growth substances ▪ ischemia ▪ angina ▪ heart disease

Angiogenesis is the growth and proliferation of new blood vessels from existing vasculature. The use of angiogenic growth factors to promote the growth of collateral blood vessels in ischemic tissue has been termed therapeutic angiogenesis. Vascular endothelial growth factor (VEGF) is a family of angiogenic growth factors specific for endothelial cells.\(^1,2\) Successful therapeutic angiogenesis has been reported with VEGF protein or genes that encode VEGF in preclinical models.\(^3-8\) Initial clinical trials in patients with myocardial ischemia\(^9-16\) and peripheral vascular disease\(^17\) have been encouraging but have enrolled small numbers of patients, and few had placebo controls. Three recent double-blind, placebo-controlled trials utilizing intracoronary fibroblast growth factor (FGF)-2 protein,\(^18\) intracoronary adenovirus encoding FGF-4,\(^19\) and intramyocardial plasmid encoding VEGF-2\(^20\) demonstrated modest clinical benefits. Initial clinical trials using intracoronary\(^9,10\) and intravenous\(^2\) recombinant VEGF\(_{165}\) protein (rhVEGF) demonstrated safety, tolerability, and encouraging clinical results. These trials led to the VIVA trial (Vascular endothelial growth
factor in Ischemia for Vascular Angiogenesis), a double-blind, placebo-controlled trial designed to determine the safety and efficacy of intracoronary and intravenous rhVEGF for therapeutic angiogenesis in patients with chronic myocardial ischemia not amenable to standard revascularization techniques.

**Methods**

**Patients**

The study was reviewed by the appropriate institutional review boards and was conducted in accordance with the Helsinki Declaration of 1975 (revised 1983). Eligible patients were 40 to 75 years of age with stable exertional angina and areas of viable but underperfused myocardium according to perfusion imaging, who were judged unsuitable for revascularization on the basis of coronary angiography within the previous 6 months. Patients were required to exercise between 3 and 11 minutes on an exercise treadmill test (ETT). Exclusion criteria included unstable angina, myocardial infarction or CABG within the previous 6 months, PCI within the previous 3 months, previous myocardial laser revascularization or angiogenic growth factor treatment, ejection fraction <25%, pregnancy, history of cancer within the previous 5 years, proliferative retinopathy or macular degeneration, renal insufficiency, or other severe concurrent illness.

**Study Procedures**

Clinical evaluations, blood chemistries, and quality of life (QOL) assessments (Seattle Angina Questionnaire [SAQ], the Short Form-36 [SF-36] and the Duke Activity Scale Index [DASI]) were completed at baseline, day 60, and day 120. Retinal photographs were obtained at baseline and day 120. Patients underwent an ETT with myocardial perfusion imaging at baseline and day 60 (±4), and without imaging at day 120 (±5). Medications were kept constant throughout the treatment period.

**Treatment Regimen**

Patients were randomized to receive a 20-minute intracoronary infusion of placebo, low-dose rhVEGF (17 ng · kg⁻¹ · min⁻¹), or high-dose rhVEGF (50 ng · kg⁻¹ · min⁻¹) followed by 4-hour intravenous infusion on days 3, 6, and 9.

**Myocardial Perfusion Imaging**

The protocol consisted of a rest thallium-201 scan and gated rest technicium-99 m-sestamibi scan followed by a nongated redistribution thallium-201 scan and a gated stress sestamibi on day 2. A modified Bruce protocol to maximal exercise off medications (β-blockers held ≥24 hours) was utilized with day-60 injection of sestamibi at the same heart rate as the baseline ETT to assess myocardial perfusion at a similar workload. Summed stress and rest scores were calculated according to a 20-segment model (range from 0 [normal activity] to 4 [no activity]).

**Statistical Analysis**

The primary end point of the study was change in ETT time from baseline to day 60 between groups. Secondary end points included change in ETT time from baseline to day 120, rest and exercise myocardial perfusion imaging on day 60, and angina class and QOL measurements at days 60 and 120.

Primary analysis was based on intention to treat. Patients who died or were lost to follow-up were assigned least rank in the ETT analysis, and groups were compared with the Wilcoxon rank-sum test. Because the change in ETT time was not normally distributed, median values were used. Analysis for changes in angina class was performed by using an exact linear-by-linear association test with no adjustment for the 2 patients who died. Statistical analysis was performed with the use of SAS statistical software. All statistical tests were two-sided and conducted at the 0.05 level of significance.

**Results**

**Baseline Characteristics**

A total of 178 subjects were enrolled at 33 trial sites (see Appendix) from April through December 1998. Sixty-three patients received placebo, 56 patients low-dose (17 ng · kg⁻¹ · min⁻¹) rhVEGF, and 59 patients high-dose (50 ng · kg⁻¹ · min⁻¹) rhVEGF. Baseline characteristics are shown in Table 1. There were no significant differences between the three groups. As expected, there was a high frequency of previous myocardial infarction, revascularization, and use of cardiovascular medications in this cohort of patients. More patients receiving high-dose rhVEGF had diabetes (39%) compared with the placebo group (30%) (P=0.30).

**Safety and Tolerability**

Infusion of rhVEGF was well tolerated by all groups. The maximal percent decrease in systolic blood pressure with each infusion is shown in Table 2. Although the decrease in systolic blood pressure was greater in rhVEGF-treated patients, the changes were modest and transient, and only 1 patient (high-dose group) had severe hypotension (chest pain with systolic pressure <100 mm Hg, which resolved with hydration).

In previous trials, a flushing reaction was noted. In VIVA, flushing occurred at least once in 35% of placebo patients, 74% of the low-dose patients, and 90% of the high-dose patients.

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics</th>
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<tr>
<td>Age, mean±SD</td>
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<tr>
<td>Male sex, %</td>
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<tr>
<td>Myocardial infarction, %</td>
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<tr>
<td>PCI, %</td>
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<td>CABG, %</td>
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<td>Diabetes mellitus, %</td>
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<td>Smoking, %</td>
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<td>Ever</td>
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<td>Hypertension, %</td>
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<td>Aspirin, %</td>
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<td>Nitrates, %</td>
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<tr>
<td>β-Blockers, %</td>
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<tr>
<td>Calcium channel blockers, %</td>
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<tr>
<td>ACE inhibitors, %</td>
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<td>Statins, %</td>
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</table>

The sample size estimate for the primary end point of change in ETT time was based on previous studies in similar populations. Assuming a change in ETT time of 2 minutes with a standard deviation of 3.3 minutes, a sample size of 50 subjects in each of three groups would provide 90% power to detect a 2-minute difference between treatment and placebo equivalent at the 0.05 level of significance.
There were no clinically significant changes from baseline within or between groups in serum electrolytes, chemistries, hematologic parameters, or urinalysis. In addition, there was no increase in adverse events in rhVEGF-treated patients, including thrombocytopenia, proteinuria or renal insufficiency, allergic reactions, worsening of congestive heart failure, pleural effusions, or pedal edema.

Clinical Events
Overall, there was no difference in clinical event rates across all three groups during the 120-day study period (Table 3). Two deaths occurred, both in the placebo group. Despite careful baseline screening, 3 patients were diagnosed with new cancers, all in the placebo group. One patient in the placebo group developed severe myocardial ischemia with cardiogenic shock on day 7. Only 1 patient (placebo treated with preexisting diabetes) developed macular edema.

Exercise Results
The baseline exercise duration was similar between the three groups: placebo group, 7.8 ± 2.8 minutes; low-dose group, 7.7 ± 2.2 minutes; and high-dose group, 7.6 ± 2.5 minutes. The median change from baseline with individual data is shown in Figure 1. There was no evidence of a treatment effect on the primary end point, change in ETT time from baseline to day 60. From day 60 to day 120, the median change in ETT time declined from 48 to 24 and 30 to 18 seconds in the placebo and low-dose rhVEGF patients, respectively. In contrast, high-dose rhVEGF-treated patients improved from 30 seconds at day 60 to 48 seconds at day 120, a significant improvement from baseline (P=0.01). This resulted in a favorable trend at day 120 in high-dose rhVEGF-treated patients compared with placebo (48 versus 24 seconds, P=0.15) (Figure 2).

Angina/Quality of Life
The distribution of Canadian Class angina at baseline is shown in Figure 3A. The mean angina class at baseline was 2.8 ± 0.7 in the placebo group, 2.6 ± 0.8 in the low-dose rhVEGF-treated group, and 2.6 ± 0.9 in the high-dose rhVEGF-treated group. Complete follow-up data were achieved in all but 3 patients (2 deaths). Although all three groups demonstrated a significant improvement in angina class from baseline to day 60, there was no significant difference between groups (Figure 3B). As with ETT time, there was a loss of benefit in placebo patients from days 60 to 120, with ongoing improvement in high-dose rhVEGF-treated patients. This resulted in a significant improvement in angina class for high-dose rhVEGF-treated patients compared with placebo at day 120 (P=0.05) (Figures 2 and 3C). The mean angina class for placebo, low-dose rhVEGF, and high-dose rhVEGF was 2.0 ± 0.8, 1.9 ± 0.8, and 1.8 ± 0.9 at

<table>
<thead>
<tr>
<th>TABLE 2. Maximal Percent Decrease in Systolic Blood Pressure</th>
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<td><strong>Placebo</strong></td>
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<td>---</td>
</tr>
<tr>
<td>IC</td>
</tr>
<tr>
<td>IV No. 1</td>
</tr>
<tr>
<td>IV No. 2</td>
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<td>IV No. 3</td>
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</tbody>
</table>

Values given as mean ± SD. IC indicates intracoronary infusion; IV, intravenous infusion.

*P < 0.001 vs placebo.

<table>
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<tr>
<th>TABLE 3. Clinical Events</th>
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<tbody>
<tr>
<td><strong>Placebo</strong></td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Revascularization</td>
</tr>
<tr>
<td>Angina hospitalization</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Ophthalmological changes</td>
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</tbody>
</table>
Changes From Baseline To Day 60 & Day 120

Clinically significant improvements were seen in all 3 groups for all 5 domains of the SAQ at day 60, but there was no significant difference between groups. The most striking improvements were seen in angina stability and angina frequency. Similar findings were seen for the SF-36 assessment of physical function and the DASI. As with ETT time and angina class, there was less benefit in placebo patients at day 120 and ongoing improvement in the high-dose rhVEGF group. The changes from baseline to day 60 and to day 120 for the angina frequency domain of the SAQ are shown in Figure 3 (day-120 placebo versus high-dose rhVEGF, \( P<0.09 \)). At day 120, physical function on SF-36 was improved in the high-dose rhVEGF patients compared with placebo (\( P<0.05 \)).

**Myocardial Perfusion**

Myocardial perfusion at stress, rest, and redistribution was performed to assess areas of viable, infarcted, ischemic, and hibernating myocardium. No significant improvement was seen in the summed rest or summed stress scores at day 60 (Table 4). Likewise, there was no significant improvement in the resting or post-stress ejection fraction.

**Discussion**

The VIVA trial is the first randomized, double-blind, placebo-controlled trial using rhVEGF for therapeutic angiogenesis. The primary end point of the trial, change in ETT time from baseline to day 60, was negative. At day 60, all three groups had improvements from baseline in angina class and QOL measurements, but there was no significant difference between groups. At day 120, there was less benefit in the placebo group and ongoing improvement in the high-dose rhVEGF-treated patients, resulting in a significant improvement in angina class at day 120 as well as favorable trends for ETT time and QOL. This may suggest a dose-dependent effect of rhVEGF. rhVEGF seems to be well tolerated, with excellent short-term safety. Results of this trial have important implications for the design of subsequent trials in the field of therapeutic angiogenesis.

**Previous Trials of Coronary Angiogenesis**

Initial angiogenic growth factor trials generated considerable excitement with regard to therapeutic angiogenesis for patients with severe myocardial ischemia not amenable to revascularization. Encouraging clinical results were reported in small trials (without control patients) using intramyocardial gene therapy with a plasmid encoding VEGF165,12 an adenovirus encoding VEGF121,13 and intracoronary FGF-2 protein.15 Two small trials using FGF protein in conjunction with CABG11,14 suggested clinical benefits. Recently, three double-blind, placebo-controlled clinical trials using intracoronary FGF-2 protein, intracoronary FGF-4 gene therapy, and intramyocardial VEGF-2 gene therapy have reported excellent short-term safety with modest clinical benefits, especially in particular patient subgroups.18–20 Despite these promising initial results, the long-term efficacy and safety of angiogenic growth factors need to be established in large placebo-controlled trials.

**Previous Trials With rhVEGF**

In the initial experience with rhVEGF, 15 patients received 20-minute intracoronary infusions (5, 17, 50, or 167 ng · kg\(^{-1}\) · min\(^{-1}\)).9 The maximum tolerated dose was identified as 50 ng · kg\(^{-1}\) · min\(^{-1}\) with a decrease in blood pressure at the 167–ng · kg\(^{-1}\) · min\(^{-1}\) dose. Although there was no change in the summed stress score, at day 60 there was a significant improvement in the summed rest score in the high-dose VEGF group at 14.7 versus 10.7 (\( P<0.05 \)).10 All 7 patients with follow-up angiograms had a significant improvement in collateral density score. In addition, 13 of the 15 patients had a significant decrease in angina class (\( P=0.002 \)).

In a second trial, 28 patients received intravenous rhVEGF (17 to 100 ng · kg\(^{-1}\) · min\(^{-1}\) for 1 to 4 hours).7 As in the intracoronary trial, 50 ng · kg\(^{-1}\) · min\(^{-1}\) was the maximally...
tolerated dose, on the basis of the decrease in systolic pressure with 100 ng·kg⁻¹·min⁻¹. Myocardial perfusion imaging improved in at least 2 segments by 2 perfusion grades in 54% of patients and was more impressive in resting perfusion, as with the intracoronary trial. More collaterals were seen in 38% of patients at 60-day angiographic follow-up. In both trials, rhVEGF165 was well tolerated with no significant adverse events.

**Safety**

Concern exists about pathological angiogenesis, such as accelerated growth of malignant tumors, retinopathy, or progression of atherosclerosis, with the use of angiogenic growth factors. Results of this trial indicate excellent short-term safety with rhVEGF165. Both infusions were well tolerated, with only one episode of severe hypotension and no other acute adverse events. No patient treated with rhVEGF developed cancer or ophthalmological abnormalities. There was no evidence for progression of atherosclerosis by angiography and no deaths or myocardial infarctions in patients treated with rhVEGF. Further assurances of safety will require a larger number of patients treated with a longer-term follow-up, but these results are encouraging as we identify the ideal target population and develop methods to improve efficacy.

**Efficacy**

The primary end point of the trial, powered to detect a 2-minute improvement in rhVEGF-treated patients compared with placebo, was negative. At day 120, the improvement in ETT time was 48 seconds for 50 ng·kg⁻¹·min⁻¹ rhVEGF compared with 24 seconds for placebo patients. These increases are modest in comparison to previous Phase I trials without placebo control groups. For example, Laham et al reported a 123-second improvement in ETT time at day 180 with intracoronary FGF-2 protein, and Symes et al reported a 170-second improvement at day 180 with intramyocardial plasmid encoding VEGF165.

Angina measured by angina class and angina frequency on the SAQ was significantly improved in all 3 groups at day 60, but the difference between groups was not statistically significant. As with ETT time, the benefit in the placebo group was diminished at day 120 for both angina class and angina frequency. At the same time, the high-dose rhVEGF-treated patients continued to improve from days 60 to 120. This resulted in a significant improvement in angina class at day 120 (P<0.05), a prespecified secondary end point. Angina frequency as reported by SAQ was consistent with the results of angina class, with a favorable trend (P=0.09) toward improvement at day 120. The improvement in angina frequency for high-dose rhVEGF patients at day 120 was 23, only slightly less than results with PTCA.

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**TABLE 4. Myocardial Perfusion and Function Results at Day 60**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low-Dose rhVEGF</th>
<th>High-Dose rhVEGF</th>
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<tbody>
<tr>
<td>Summed stress score n</td>
<td>56</td>
<td>54</td>
<td>59</td>
</tr>
<tr>
<td>Baseline</td>
<td>15.4±4.3</td>
<td>10.3±7.1</td>
<td>16.2±9.3</td>
</tr>
<tr>
<td>Day 60</td>
<td>14.0±10.0</td>
<td>16.0±9.5</td>
<td>17.2±12.1</td>
</tr>
<tr>
<td>Summed rest score n</td>
<td>58</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.0±7.7</td>
<td>5.5±6.0</td>
<td>5.9±9.6</td>
</tr>
<tr>
<td>Day 60</td>
<td>6.1±7.5</td>
<td>5.7±6.2</td>
<td>6.1±10.1</td>
</tr>
<tr>
<td>Resting ejection fraction</td>
<td>52±12.5</td>
<td>50±11.2</td>
<td>51±13.9</td>
</tr>
<tr>
<td>Baseline</td>
<td>51±10.9</td>
<td>50±11.6</td>
<td>50±13.1</td>
</tr>
<tr>
<td>Day 60</td>
<td>47±12.2</td>
<td>47±12.0</td>
<td>47±13.0</td>
</tr>
</tbody>
</table>

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Figure 3. Distribution of Canadian Class Angina for placebo, low-dose, and high-dose treated VEGF patients at baseline (A), day 60 (B), and day 120 (C).

Angina measured by angina class and angina frequency on the SAQ was significantly improved in all 3 groups at day 60, but the difference between groups was not statistically significant. As with ETT time, the benefit in the placebo group was diminished at day 120 for both angina class and angina frequency. At the same time, the high-dose rhVEGF-treated patients continued to improve from days 60 to 120. This resulted in a significant improvement in angina class at day 120 (P<0.05), a prespecified secondary end point. Angina frequency as reported by SAQ was consistent with the results of angina class, with a favorable trend (P=0.09) toward improvement at day 120. The improvement in angina frequency for high-dose rhVEGF patients at day 120 was 23, only slightly less than results with PTCA.
At day 120, 45% of high-dose rhVEGF-treated patients had class 0 to 1 angina, compared with 23% of placebo-treated patients. Likewise, the number of patients who had class 3 or 4 angina in the placebo group was double that of the patients treated with high-dose VEGF (35% versus 15%).

In contrast to uncontrolled Phase I trials, there were no improvements in myocardial perfusion at day 60. The summed rest score in VIVA was 5.9 compared with 14.7 in the Phase I trial for patients treated with 50 ng · kg⁻¹ · min⁻¹, perhaps indicating a healthier patient population. If the predominant benefit of angiogenic therapy is seen in patients with resting perfusion defects, as previously reported, this may explain the lack of benefits seen at day 60. A modest increase in collateral blood flow may be insufficient to prevent ischemia at peak exercise off β-blockers as performed in this trial. Unfortunately, myocardial perfusion imaging was not performed at day 120; therefore, it is unknown whether the improvements noted at day 120 in the high-dose rhVEGF-treated patients were associated with changes in myocardial perfusion.

**Placebo Effect**

An important finding of this trial is the prominent placebo effect noted at day 60 with a 48-second improvement in ETT time, 56% of patients improving at least one angina class, and a nearly 14-point improvement in SAQ angina frequency domain. Although these benefits were diminished at day 120, 47% of patients had a persistent improvement in angina class. To the best of our knowledge, there were no changes in medical therapy or smoking status during the course of the trial, and only 1 placebo patient underwent revascularization.

Although the improvement noted in the placebo group emphasizes the need for caution in the interpretation of positive results of uncontrolled trials, the adverse events in the placebo group serve to highlight another critical aspect of placebo-controlled trials. Despite extensive baseline screening, 3 patients in the placebo group developed cancer over the course of the 120-day trial. Likewise, the only 2 deaths and the only ophthalmological changes occurred in placebo patients. This clearly illustrates the importance of a placebo group in interpretation of both positive and negative results.

**Time Course of Angiogenesis**

The patients treated with 50 ng · kg⁻¹ · min⁻¹ of rhVEGF demonstrated an improvement in ETT time, angina class, and SAQ angina frequency from day 60 to 120. Although successful angiogenesis has been demonstrated in preclinical models, these have, in general, been short-term models, and little is known about the long-term efficacy of angiogenic growth factors. One trial in a porcine model using intravenous rhVEGF demonstrated a significant improvement in myocardial function at 6 months compared with 3 months. The ongoing improvement noted in the VIVA trial is similar to other trials with rhVEGF: for example, the plasmid-encoding VEGF₁₆₅ with 33%, 44%, and 60% of patients free of angina at 2, 3, and 6 months, respectively.

**Explanation/Limitations**

Despite the excellent safety profile of rhVEGF and an improvement in several secondary end points at day 120, these results are disappointing. Potential explanations include suboptimal dose or route of administration, a healthier population of patients enrolled, or lack of efficacy using this dose and route of administration of VEGF₁₆₅ protein. The ideal end point and time points for assessment of benefit in therapeutic angiogenesis trials is still unclear. For example, time to angina or ST depression and the percentage of patients limited by angina were not prespecified end points in VIVA but may add insight into the ETT results. Finally, more preclinical data are needed with regard to the time course of angiogenesis, the ideal growth factor, and the optimal dose and route of administration.

**Conclusion**

In conclusion, intracoronary plus intravenous rhVEGF was well tolerated with excellent short-term safety. There was no evidence for a treatment effect on the primary end point, change in ETT time from baseline to day 60, and no improvements in myocardial perfusion. A prominent placebo effect was present at day 60 but was diminished by day 120. Patients treated with high-dose VEGF had a significant improvement in angina class at day 120. Although this is the first randomized, controlled trial of VEGF for therapeutic angiogenesis, it is still a relatively small trial with a short-term follow-up. Larger trials with longer-term follow-up are required to determine the long-term efficacy and safety of VEGF. Finally, trials using alternative growth factors, dose regimens, and methods of delivery, including sustained release and gene transfer, are needed to enhance the treatment benefit of angiogenic growth factors in patients with severe myocardial ischemia who are not optimal candidates for standard revascularization techniques.

**Appendix**

In addition to the authors, the following persons were members of the VIVA study group: Hennepin County Medical Center, Minneapolis, Minn; Boisjolie; Durham VA and Duke University, Durham, NC; Landis; C. Martz; Rhode Island Hospital, Providence, L. Donahue; University of Connecticut Health Center, Farmington, M.B. Barry; University of Iowa, Iowa City; M. Costigan; University of California San Diego, J. Van Dijk; Cedars-Sinai Medical Center, Los Angeles, Calif; M. Gheorghiu; Hermann Hospital, Houston, Tex; L. Weigelt; Mt Sinai, New York, NY; I. Guzman; Northwestern University, Chicago, Ill, R. Hendel, B. Toth; University of Alabama, Birmingham, C. Ritondo; University of California at Davis, R. Valente, B. Pierce; New England Medical Center, Boston, Mass, J. Smith, R. Miele; Prairie Heart Institute, Springfield, Ill; S. Ellis, K. Comella; Minneapolis VA Medical Center, Minn, A. From, L. Bass; Stanford University School of Medicine, Palo Alto, Calif; J. Giacomini, V. Sharma; Cleveland Clinic Heart Center, Ohio, S. Ellis, K. Comella; Minneapolis VA Medical Center, Minn, A. From, L. Bass; Stanford University School of Medicine, Palo Alto, Calif; J. Cooke, S. Rockson, L. Lissim; Texas Heart Institute, Houston, J. Willerson, M. Harlan; Baylor College, Houston, Tex; N. Kleinman, K. Maresh; Crawford Long Hospital of Emory University, Atlanta, Ga; J. Marshall, K. Moehring; Henry Ford Hospital, Detroit, Mich, P. Kraft, M. Fox; University of Southern California, Los Angeles, D. Faxon, I. Gutierrez; University of Virginia, Charlottesville, L. Sarembock, L. Snyder; Winthrop Hospital, Mineola, NY; R. Steingart, S. Parker; Arizona Heart Institute, R. Stumpf, S. Spooner; Atlanta VA, Ga; J. Marshall, A. Lane; Hartford Hospital, Hartford, Conn, J. Cloutier; MCO of Ohio, Toledo, D. Weisshaar, D. Stewart; Sequoia Hospital, Redwood City, Calif; T. Hinohara, M. Johnson; Genentech Inc, South San Francisco, Calif; C. Luce, T. Tu, D. Bisio, J. Kuczma; University of Wisconsin Ophthalmology Core.
Laboratory, R. Klein, M. Neider, S. Meuer; Perfuse Core Laboratory, K. Ryan; and Cedar-Sinai Nuclear Cardiology, H. Lewin, L. Miranda.

References

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